Evoke Pharma Inc
Form 10-K
March 06, 2019

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, DC 20549

Form 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2018

or

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission file number: 001-36075

Evoke Pharma, Inc.

(Exact Name of Registrant as Specified in its Charter)

Delaware	20-8447886
(State or Other Jurisdiction of	(I.R.S. Employer
Incorporation or Organization)	Identification No.)
420 Stevens Avenue, Suite 370	
Solana Beach, California	92075
(Address of Principal Executive Offices)	(Zip Code)

858-345-1494

(Registrant's Telephone Number, Including Area Code)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, par value $0.0001 per share	The Nasdaq Capital Market

Securities registered pursuant to Section 12(g) of the Act:

None

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

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

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

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of the 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 emerging growth company. See definitions of "large accelerated filer," "accelerated filer," "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

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

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

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Securities Exchange Act of 1934). Yes No

The aggregate market value of the registrant's common stock held by non-affiliates of the registrant as of the last business day of the registrant's most recently completed second fiscal quarter was approximately $39.8 million, based on the closing price of the registrant's common stock on the Nasdaq Capital Market of $2.50 per share.

The number of outstanding shares of the registrant's common stock, par value $0.0001 per share, as of February 28, 2019 was 17,427,533.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement to be filed with the Securities and Exchange Commission pursuant to Regulation 14A in connection with the registrant's 2019 Annual Meeting of Stockholders, which will be filed subsequent to the date hereof, are incorporated by reference into Part III of this Form 10-K. Such proxy statement will be filed with the Securities and Exchange Commission not later than 120 days following the end of the registrant's fiscal year ended December 31, 2018.

EVOKE PHARMA, INC.

FORM 10-K — ANNUAL REPORT

For the Fiscal Year Ended December 31, 2018

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PART I

Forward-Looking Statements and Market Data

This Annual Report on Form 10-K contains "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and 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 Annual Report on Form 10-K, including statements regarding our future results of operations and financial position, business strategy, prospective products, product approvals, such as the new drug application for Gimoti which has been filed with the U.S. Food and Drug Administration, regulatory developments, research and development costs, timing and likelihood of success, 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 statement. The forward-looking statements are contained principally in the sections entitled "Risk Factors," "Management's Discussion and Analysis of Financial Condition and Results of Operations" and "Business." In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "anticipat "could," "intend," "target," "project," "contemplates," "believes," "estimates," "predicts," "potential" or "continue" or the nega terms or other similar expressions. Although we believe the expectations reflected in these forward-looking statements are reasonable, such statements are inherently subject to risk and we can give no assurances that our expectations will prove to be correct. Given these risks, uncertainties and other factors, you should not place undue reliance on these forward-looking statements, which speak only as of the date of this Annual Report on Form 10-K. You should read this Annual Report on Form 10-K completely. As a result of many factors, including without limitation those set forth under "Risk Factors" under Item 1A of this Part I below, and elsewhere in this Annual Report on Form 10-K, our actual results may differ materially from those anticipated in these forward-looking statements. Except as required by applicable law, we undertake no obligation to update these forward-looking statements to reflect events or circumstances after the date of this report or to reflect actual outcomes. For all forward-looking statements, we claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

This Annual Report on Form 10-K also contains estimates, projections and other information concerning our industry, our business, and the markets for Gimoti™ (metoclopramide nasal spray), including data regarding the estimated size of those markets, their projected growth rates, the incidence of certain medical conditions, statements that certain drugs or classes of drugs are the most widely prescribed in the United States or other markets, the perceptions and preferences of patients and physicians regarding certain therapies and other prescription, prescriber and patient data, as well as data regarding market research, estimates and forecasts prepared by our management. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources.

We use our registered trademark, EVOKE PHARMA, and our trademarked product name, GIMOTI, in this Annual Report on Form 10-K. This Annual Report on 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 Annual Report on Form 10-K appear without the ® and ™ symbols, but those references are not intended to indicate, in any way, 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.

Unless the context requires otherwise, references in this Annual Report on Form 10-K to "Evoke," "we," "us" and "our" refer to Evoke Pharma, Inc.

Item 1. Business

Overview

We are a specialty pharmaceutical company focused primarily on the development of drugs to treat gastrointestinal, or GI, disorders and diseases. We are developing Gimoti, an investigational metoclopramide nasal spray for the relief of symptoms associated with acute and recurrent diabetic gastroparesis in women. Diabetic gastroparesis is a GI disorder afflicting millions of individuals worldwide and is characterized by slow or delayed gastric emptying and evidence of gastric retention in the absence of mechanical obstruction and can cause various serious digestive system symptoms and other complications. Metoclopramide tablets and injection are the only products currently approved in the United States to treat the symptoms associated with acute and recurrent diabetic gastroparesis. Gimoti is a novel nasal spray formulation of metoclopramide designed to provide systemic delivery of the molecule through the nasal mucosa. We submitted a New Drug Application, or NDA, for Gimoti to the U.S. Food and Drug Administration, or FDA, on June 1, 2018 and received a Day-74 FDA filing communication letter in August 2018. The letter stated that the NDA was sufficiently complete to permit a substantive review and set a target goal date under the Prescription Drug User Fee Act, or PDUFA, of April 1, 2019. On March 1, 2019, we received a multi-disciplinary review letter, or DRL, from FDA, which provided preliminary

notice of certain deficiencies identified during FDA's initial review of the Gimoti NDA. Specifically, the DRL described concerns with the information provided in the NDA, including concerns that insufficient evidence had been offered regarding product quality control and reproducibility specific to the commercially available sprayer device used with Gimoti, that there is a lack of adequate information to support sex-based efficacy claims and that the pharmacology data provided may not demonstrate bioavailability to the Listed Drug, Reglan Tablets10 mg. Although a DRL reflects preliminary comments that are subject to change and does not reflect FDA's final decision on the NDA, approval of Gimoti by the PDUFA date of April 1, 2019, if any, is uncertain given the letter. We plan to respond to the deficiencies raised in the DRL to allow time for FDA to potentially complete its review prior to the PDUFA date. However, there is no guarantee that we will be able to adequately address these deficiencies to FDA's satisfaction or that FDA will be able to consider our response before it takes final action on the NDA. The receipt of the DRL increases the risk that we may receive a complete response letter, or CRL, based on the deficiencies raised in the DRL or other issues identified by FDA as it completes its review of the NDA.

In individuals with gastroparesis, food remains in the stomach for a longer time than normal, leading to a variety of GI symptoms and systemic metabolic complications. Gastroparesis frequently occurs in individuals with diabetes, but is also observed in patients with prior gastric surgery, a preceding infectious illness, pseudo-obstruction, collagen vascular disorders and anorexia nervosa. In some patients with gastroparesis, no cause can be identified, which is referred to as idiopathic gastroparesis. According to the American Motility Society Task Force on Gastroparesis, the prevalence of gastroparesis is estimated to be up to 4% of the United States population. Signs and symptoms of gastroparesis may include nausea, early satiety, bloating, prolonged fullness, upper abdominal pain, vomiting and retching. Patients may experience any combination of signs and symptoms with varying degrees of severity.

Patients with diabetic gastroparesis may experience impaired glucose control due to unpredictable gastric emptying and altered absorption of orally administered hypoglycemic drugs, which may affect the severity of their signs and symptoms. Severe signs and symptoms may cause complications such as malnutrition, esophagitis, and Mallory Weiss tears. Gastroparesis adversely affects the lives of patients with the disease, resulting in decreased social interaction, poor work functionality, and the development of anxiety and/or depression.

We believe nasal spray administration has the potential to provide our target population of female diabetic gastroparesis patients with a preferred treatment option over the tablet formulation for several important reasons: (1) unlike metoclopramide tablets which may be absorbed erratically due to gastroparesis itself, Gimoti is designed to bypass the digestive system to allow for more predictable absorption without needing to determine if a patient's stomach is functioning; (2) during episodes of vomiting Gimoti provides predictable drug absorption through the nasal mucosa; and (3) for gastroparesis patients experiencing nausea and are not wanting to swallow a pill or water, a nasal spray may be better tolerated than an oral medication.

We have evaluated Gimoti in a multicenter, randomized, double-blind, placebo-controlled parallel group, dose-ranging Phase 2b clinical trial in 287 male and female subjects with diabetic gastroparesis where Gimoti doses of 10 mg and 14 mg were effective in improving the characteristic and clinically-relevant symptoms associated with gastroparesis in women while exhibiting a favorable safety profile in men and women. Subjects received either Gimoti or placebo four times daily for 28 days.

In July 2016, we announced results from a Phase 3 clinical trial of Gimoti in female subjects with symptoms associated with acute and recurrent diabetic gastroparesis. This trial was a multicenter, randomized, double-blind, placebo-controlled, parallel group clinical trial to evaluate the efficacy, safety and population pharmacokinetics, or PK, of 10 mg Gimoti in adult female subjects with symptomatic diabetic gastroparesis and delayed gastric emptying determined by gastric emptying scintigraphy, or GES. Subjects received either Gimoti or placebo four times daily for 28 days. The primary endpoint was the change in symptoms from the baseline period to Week 4 as measured using a proprietary Patient Reported Outcome, or PRO, instrument. On a daily basis, subjects reported the frequency and severity of their gastroparesis signs and symptoms using a telephone diary. The subjects' daily symptom scores were the basis for calculating their weekly scores using the PRO instrument. A total of 205 subjects were randomized in

this trial. Results of the trial showed that Gimoti did not achieve its primary endpoint of a symptom improvement at Week 4 in the intent to treat, or ITT, population.

Although the Phase 3 trial failed to achieve its primary endpoint, Gimoti demonstrated efficacy in patients with moderate to severe symptoms at baseline, which included 105 of the 205 patients (51%) enrolled in the study. In these patients with higher symptom severity, statistically significant benefits were demonstrated for those treated with Gimoti versus those receiving placebo. These statistically significant benefits were observed at Weeks 1, 2 and 3 in the ITT population and at all four weeks in the per protocol population. There were also clinically and statistically significant improvements in nausea and upper abdominal pain, two of the more severe and debilitating symptoms of gastroparesis, at all four weeks.

We have also conducted a companion clinical trial with Gimoti in male subjects with symptoms associated with acute and recurrent diabetic gastroparesis to assess the safety and efficacy of Gimoti in men. The male companion trial was initiated in April 2014 and the design was the same as the Phase 3 trial in women. This companion trial was requested by FDA to confirm the Phase 2b trial results and to capture additional safety data in men. As anticipated, the available data confirmed the Phase 2b results that showed Gimoti was

well-tolerated, but showed no statistically significant efficacy in men. In addition, the safety profile for Gimoti was favorable compared to placebo with good tolerability.

In December 2016, we had a pre-NDA meeting with FDA, in which FDA agreed that a comparative exposure PK trial was acceptable as a basis for submission of a Gimoti NDA. In March 2017, we had a type A meeting with FDA to finalize the design of the comparative exposure PK trial and reach agreement on certain other chemistry, manufacturing and controls-related items associated with the NDA submission.

In October 2017, we announced positive topline results from the comparative exposure PK trial. The objective of the trial was to identify a dose of Gimoti that met the criteria for bioequivalence compared to the Listed Drug, Reglan Tablets 10 mg., after nasal and oral administration to healthy volunteers under fasted conditions.

The comparative exposure PK trial was an open label, 4-way crossover and enrolled 108 healthy male and female volunteers who each received one Reglan Tablet dose and three different doses of Gimoti in a random sequence. Following discussions at pre-NDA meetings with FDA, we planned to select a Gimoti dose based on criteria that included a 90% confidence interval for the ratio of area under the plasma concentration curve, or AUC, falling within the exposure equivalence range of 80-125% of the Listed Drug, Reglan Tablets 10 mg. Though only one dose was needed to meet the dose selection criteria, the comparative exposure PK trial was designed to test three different doses of Gimoti. Based on results of the study, two of the three doses tested met the dose selection criteria for the pooled data in women and men. The maximum observed plasma concentration, or C_{max}, for Gimoti was slightly lower than the equivalence range, which we had anticipated and previously discussed with FDA as a likely outcome given the different route of administration and prior Gimoti PK trial results. Additionally, data showed the AUC and C_{max} increased in a dose-related manner across all three Gimoti doses tested. Relative to safety, all Gimoti doses were well tolerated with no serious or clinically significant adverse events reported following any of the doses.

Additional analysis of the PK data by sex revealed statistically significant differences in exposure between women and men given the same metoclopramide dose (both nasal and oral). Further analysis of results from the comparative exposure PK trial found statistically significantly lower AUC's in men compared to women. Similar sex-based differences were also observed irrespective of the route of metoclopramide administration (nasal, oral and IV) in one of our previous healthy volunteer studies.

In the most recent comparative exposure PK trial, results for women independently met equivalence criteria for $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ at the Gimoti dose proposed in the NDA. We submitted the NDA for a female-only indication based on a dose in women with equivalent exposure to the Listed Drug, Reglan Tablets 10 mg. and submitted supporting efficacy and safety data from our Phase 2b and Phase 3 trials at doses similar or lower than the dose proposed in the NDA.

In January 2018, we had a final pre-NDA meeting with FDA to discuss and clarify FDA's expectations for items being prepared for inclusion in the NDA for Gimoti. Based on the discussion and feedback from the FDA meeting, the NDA included a risk management strategy and a proposal for a post-approval safety study designed to confirm prior safety findings and compare Gimoti side effects with those of the Listed Drug, Reglan Tablets 10 mg. We expect to discuss the details of the post-marketing safety trial with FDA during the NDA review process.

In March 2018, we announced that FDA granted our request for a small business waiver of the PDUFA fee of approximately $2.4 million for our 505(b)(2) NDA for Gimoti.

On January 5, 2019, we entered into a commercial services agreement, or NGP Agreement, with Novos Growth, LLC, or NGP, for the commercialization of Gimoti. Pursuant to the NGP Agreement, NGP will manage the commercial operations for a dedicated sales team to market Gimoti, if approved by FDA, to gastroenterologists and other targeted health care providers.

We have no products approved for sale, and we have not generated any revenue from product sales or other arrangements. We have primarily funded our operations through the sale of our convertible preferred stock prior to our initial public offering, or IPO, in September 2013, borrowings under bank loans and the sale of shares of our common stock on the Nasdaq Capital Market. We have incurred losses in each year since our inception. Substantially all of our operating losses resulted from expenses incurred in connection with advancing Gimoti through development activities and general and administrative costs associated with our operations. We expect to continue to incur significant expenses and increasing operating losses for at least the next several years. We may never become profitable, or if we do, we may not be able to sustain profitability on a recurring basis.

Business Strategy

Our objective is to develop and bring to market products to treat acute and chronic GI disorders that are not satisfactorily treated with current therapies and that represent significant market opportunities. Our business strategy is to:

- Pursue regulatory approval for Gimoti. We submitted the Gimoti NDA to FDA on June 1, 2018 and FDA set a PDUFA target goal date of April 1, 2019.
- Seek partnerships to accelerate and maximize the potential for Gimoti. We continue to evaluate partnering opportunities with pharmaceutical companies that have established development and sales and marketing capabilities to potentially enhance and accelerate the development and commercialization of Gimoti.
- Continue to build capabilities to potentially commercialize Gimoti in the United States. In addition to seeking partnering opportunities, we have begun to build our commercial infrastructure to allow us to directly market Gimoti in the United States, if approved by FDA. We have partnered with NGP to manage the commercial operations for a dedicated sales force to market Gimoti to gastroenterologists and other targeted health care providers. We anticipate engaging a third-party sales organization to retain, train and deploy this direct sales force or, if we are unable to reach an agreement with a third party, hire a sales force directly.
- Explore regulatory approval of Gimoti outside the United States. We are seeking approval of Gimoti in the United States and will later evaluate the market opportunity in other countries.
- Evaluate the development and/or commercialization of other therapies for GI motility disorders. Similar to our initial focus on gastroparesis, we will evaluate opportunities to in-license or acquire other product candidates, as well as commercial products, to treat patients suffering from predominantly GI disorders, seeking to identify areas of high unmet medical needs with limited treatment options.

The Gastrointestinal Market

The health of the GI system has a major effect on an individual’s daily activities and quality of life. A retrospective review published by the National Institute of Diabetes and Digestive and Kidney Diseases estimated that in 2004 there were more than 72 million ambulatory care visits with a diagnosis of a GI disorder in the United States alone. The annual cost of these GI disorders in 2004, not including digestive cancers and viral diseases, was estimated to be greater than $114 billion in direct and indirect expenditures, including hospital, physician and nursing services as well as over-the-counter and prescription drugs.

In 2004, the total cost of GI prescription drugs in the United States was $12.3 billion, and over half of this cost ($7.7 billion) was associated with drugs prescribed for gastroesophageal reflux disease, or GERD. Peptic ulcer disease, hepatitis C, irritable bowel syndrome, or IBS, and inflammatory bowel disease, or IBD, were major contributors to the remaining drug cost. Historically GI product development efforts have focused on indications with the largest patient populations such as GERD, constipation, peptic ulcers and IBS. As a result, limited innovation has occurred in other segments of the GI market, such as upper GI motility disorders, even though these disorders affect several million patients worldwide. Consequently, due to the limited treatment options available for upper GI motility disorders, we believe there is a substantial market opportunity for us to address significant unmet medical needs, initially for diabetic gastroparesis.

GI Motility Disorders

Motility disorders are some of the most common GI disorders. Motility disorders affect the orderly contractions or relaxation of the GI tract which move contents forward and prevent backward egress. This is important in the normal movement of food through the GI tract. Motility disorders are sometimes referred to as functional GI disorders to highlight that many abnormalities in stomach function can occur even when anatomic structures appear normal. Functional GI disorders affect the upper and lower GI tract and include gastroparesis, GERD, functional dyspepsia, constipation and IBS. It has been estimated by the International Foundation for Functional Gastrointestinal Disorders that one in four people in the United States suffer from functional GI disorders, having signs and symptoms such as

abdominal pain, nausea, constipation, diarrhea, bloating, decreased appetite, early satiety, swallowing difficulties, heartburn, vomiting and/or incontinence.

Gastroparesis

Gastroparesis is a debilitating, chronic condition that has a significant impact on patients' lives. It is characterized by slow or delayed gastric emptying and evidence of gastric retention in the absence of mechanical obstruction. Muscular contractions in the stomach, which move food into the intestine, may be too slow, out of rhythm or erratic. The following graph depicts the timing associated with the emptying of solids in patients with diabetic gastroparesis compared to normal individuals:

Camilleri M. New England Journal of Medicine 2007

The stomach is a muscular sac between the esophagus and the small intestine where the digestion of food begins. The stomach makes acids and enzymes referred to as gastric juices which are mixed with food by the churning action of the stomach muscles. Peristalsis is the contraction and relaxation of the stomach muscles to physically breakdown food and propel it forward. The crushed and mixed food is liquefied to form chyme and is pushed through the pyloric canal into the small intestine in a controlled and regulated manner.

In gastroparesis, the stomach does not perform these functions normally, causing characteristic flares of signs and symptoms that include nausea, early satiety, prolonged fullness, bloating, upper abdominal pain, vomiting and retching. As a result of these signs and symptoms, patients may limit their food and liquid intake leading to poor nutrition, dehydration and electrolyte disturbances, and have poor blood glucose control, ultimately requiring hospitalization. If left untreated or not adequately treated, gastroparesis causes significant acute and chronic medical problems, including additional diabetic complications resulting from poor glucose control.

Gastroparesis in the Hospital Setting

When patients experience a flare of their gastroparesis symptoms that cannot be adequately managed by oral medications, they may be hospitalized for hydration, parenteral nutrition, and correction of abnormal blood glucose or electrolyte levels. In this setting, intravenous metoclopramide is the first line of treatment. Typically, these diabetic patients with gastroparesis symptoms remain in the hospital until they are stabilized and able to be effectively treated with oral metoclopramide. These hospitalizations are costly and expose patients to increased risks, including hospital-acquired infections. The number of patients with gastroparesis that require hospitalization due to their disease is growing, according to a study published in the American Journal of Gastroenterology in 2008. Additionally, the study reported, from 1995 to 2004, total hospitalizations with a primary diagnosis of gastroparesis increased 158%. Hospital admissions for patients with gastroparesis as the secondary diagnosis increased 136%. The average length of stay for a patient is approximately six days at an estimated cost of approximately $22,000. Compared to the other four most common upper GI admission diagnoses (GERD, gastric ulcer, gastritis and nonspecific nausea/vomiting), gastroparesis had the longest length of stay and one of the highest total charges per stay. Additionally, the study estimates that costs associated with gastroparesis as the primary or secondary diagnosis for admission exceeded $3.5 billion in 2004.

A study of patients in clinics at the University of Pittsburgh Medical Center between January 2004 and December 2008, published in the Journal of Gastroenterology and Hepatology, showed that patients with diabetic or post-surgical gastroparesis had significantly more emergency room visits than other gastroparesis groups. The study reinforced the view that gastroparesis constitutes a significant burden for patients and the healthcare system, with more than one-third of patients requiring hospitalization. The number of emergency room visits and annual days of inpatient treatment were comparable to patients with Crohn’s disease. The study indicated that patients received an average of 6.7 prescriptions on admission. Eighty percent of the patients identified in the University of Pittsburgh study were women. According to a study conducted by Baylor College of Medicine and published in Gastroenterology & Endoscopy in December 2017, hospitalizations for gastroparesis have risen significantly since the early 1990s. This study noted that the number of hospitalizations increased from roughly 900 in 1994 to 16,400 in 2014, with median costs climbing from $6,000 to approximately $24,500 during the period. The number of people who visited the emergency department because of gastroparesis rose from 15,549 in 2006 to 39,470 in 2014, with an average annual increase of nearly 13% over that time.

Etiology

Gastroparesis can be a manifestation of many systemic illnesses, arise as a complication of select surgical procedures, or develop due to unknown causes. Any disease inducing neuromuscular dysfunction of the GI tract can result in gastroparesis, with diabetes being one of the leading known causes. In a 2007 study published in Current Gastroenterology Reports, 29% of gastroparesis cases were found in association with diabetes, 13% developed as a complication of surgery and 36% were due to unknown causes. According to the American Motility Society Task Force on Gastroparesis, up to 4% of the U.S. population experiences symptomatic manifestations of gastroparesis. As the incidence of diabetes rises worldwide, the prevalence of gastroparesis is expected to rise correspondingly.

The most common identified cause of gastroparesis is diabetes mellitus. The underlying mechanism of diabetic gastroparesis is unknown, though it is thought to be related in part to neuropathic changes in the vagus nerve and/or the myenteric plexus. Prolonged elevated serum glucose levels are also associated with vagus nerve damage. The vagus nerve controls the movement of food through the digestive tract and when it is damaged, movement of food through the GI tract may be abnormal. The prevalence of diabetes in the United States is rapidly rising, with the Centers for Disease Control estimating that one in ten adults currently suffer from the disease. Sedentary lifestyles, poor dietary habits and a consequent rising prevalence of obesity are expected to cause this number to grow substantially. According to a study published in the Journal of Gastrointestinal and Liver Diseases in July 2010, between 25% and 55% of type 1 and 15% and 30% of type 2 diabetics suffer from symptoms associated with the condition and diabetics are 29% of the total gastroparesis population.

A 2007 study published in Current Gastroenterology Reports states that approximately 36% of gastroparesis patients suffer from idiopathic gastroparesis. The development of idiopathic gastroparesis is thought to be related to loss of myenteric ganglion cells in the distal large bowel (myenteric hypoganglionosis) and reduction in the interstitial cells of Cajal, which help control contraction of the smooth muscle in the GI tract.

Post-surgical gastroparesis is a smaller subset of the total patient pool and accounts for approximately 13% of all cases of the disease, according to a 2007 study published in Current Gastroenterology Reports. Post-surgical gastroparesis is often associated with peptic ulcer surgery, bariatric procedures or esophageal procedures and is thought to result from damage/desensitization of the vagus nerve.

Prevalence

In 2012, the American Diabetes Association estimated that diabetes affects approximately 29.1 million people of all ages in the United States, equating to about 9.3% of the population. Based on prevalence data, the potential gastroparesis patient pool in the United States is approximately 12 to 16 million adults with women making up 82% of this population, according to a 2007 study published in Current Gastroenterology Reports.

There are approximately 2.3 million diabetic patients with moderate or severe gastroparesis symptoms who are seeking treatment in the United States by a health care professional, according to a study presented at the Digestive Disease Week 2013 conference in Orlando, Florida. When patients do receive treatment for gastroparesis, multiple medications are frequently used to address the individual signs and symptoms of gastroparesis. For example, patients may receive anti-emetics for nausea and vomiting and opioids for abdominal pain, which can exacerbate delayed gastric emptying in patients with gastroparesis.

Unmet Needs in Gastroparesis Treatment

Market research and physician interviews demonstrate that existing treatment options for diabetic gastroparesis are inadequate and there is a high level of interest in effective outpatient options for managing patients with gastroparesis symptoms. The market is currently served by oral metoclopramide, intravenous metoclopramide, and the oral disintegrating tablet, or ODT, formulation of metoclopramide (Metozolv® ODT), with approximately 4.0 million

prescriptions in the United States per year, according to IMS Health (2015).

Due to the limited availability of FDA-approved treatments for gastroparesis, physicians may resort to using medications “off-label” in an attempt to address individual symptoms experienced by patients. Off-label therapies are pharmaceuticals prescribed by physicians for an unapproved indication or in an unapproved age group, unapproved dose or unapproved form of administration. Examples of drugs used without FDA approval in gastroparesis include erythromycin and Botox® injected via endoscopic procedure directly into the lower gastric sphincter. Previously-approved drugs, such as cisapride and tegaserod, are no longer commercially available in the United States because of safety concerns. Domperidone has never been approved by FDA but is obtained through certain compounding pharmacies for individual patients under special FDA usage rules.

Gimoti is a non-oral, promotility and anti-emetic treatment that we believe has the potential to significantly improve the standard of care for female gastroparesis patients. If metoclopramide nasal spray is approved for the treatment of diabetic gastroparesis in women, patients and physicians will have access to an outpatient therapy that could be administered and absorbed even when patients are experiencing delayed gastric emptying or nausea and vomiting.

Our Solution: Gimoti (Metoclopramide Nasal Spray)

We are developing Gimoti, a dopamine antagonist / mixed 5-HT3 antagonist / 5-HT4 agonist with promotility and anti-emetic effects, for the relief of symptoms associated with acute and recurrent diabetic gastroparesis in women. Since oral metoclopramide was approved by FDA in 1980, oral and intravenous metoclopramide have been the only products approved in the United States to treat gastroparesis. Gimoti is a novel formulation of metoclopramide offering systemic delivery by nasal spray administration.

We are developing the nasal formulation of metoclopramide to provide our targeted patient population with acute or recurrent symptoms of diabetic gastroparesis with a product that can be systemically delivered as an alternative to the oral or intravenous routes of administration. Nasal delivery is possible because the mucosa of the nasal cavity is a single epithelial cell layer which is well vascularized and allows metoclopramide molecules to be transferred directly to the systemic circulation. There is no first pass liver metabolism required prior to onset of action. Since gastroparesis is a disease that halts or slows the movement of the contents of the stomach to the small intestine, oral drug administration is often compromised. The nasal formulation may also provide a predictable and consistent means of delivering metoclopramide in patients with delayed gastric emptying and/or frequent vomiting. Also, unlike the oral tablet formulation of metoclopramide, we believe that Gimoti may be tolerated even when patients are experiencing nausea.

A nasal spray formulation of metoclopramide could offer an alternative route of administration for female patients with severe symptoms of diabetic gastroparesis receiving the parenteral formulation of metoclopramide. Following hospitalization for intravenous metoclopramide, a nasal spray formulation would also provide a non-oral option for the transition to an outpatient treatment.

Comparative Exposure PK Trial

In October 2017, we announced positive topline results from the comparative exposure PK trial. The objective of the trial was to identify a dose of Gimoti that met the criteria for bioequivalence compared to the Listed Drug, Reglan Tablets 10 mg. after nasal and oral administration to healthy volunteers under fasted conditions.

The comparative exposure PK trial was an open label, 4-way crossover and enrolled 108 healthy male and female volunteers who each received one Reglan Tablet dose and three different doses of Gimoti in a random sequence. Following discussions at pre-NDA meetings with FDA, we planned to select a Gimoti dose based on criteria that included a 90% confidence interval for the ratio of AUC falling within the equivalence range of 80-125% of the Listed Drug, Reglan Tablets 10 mg. Though only one dose was needed to meet the dose selection criteria, the comparative exposure PK trial was designed to test three different doses of Gimoti. Based on results of the study, two of the three doses tested met the dose selection criteria for the pooled data in men and women. The C_{max} for Gimoti was slightly lower than the equivalence range, which we had anticipated and previously discussed with FDA as a likely outcome given the different route of administration and prior Gimoti PK trial results. Additionally, data showed the AUC and C_{max} increased in a dose-related manner across all three Gimoti doses tested. Relative to safety, all Gimoti doses were well tolerated with no serious or clinically significant adverse events reported following any of the doses.

Additional analysis of the PK data by sex revealed statistically significant differences in exposure between women and men given the same metoclopramide dose (both nasal and oral). Further analysis of results from the comparative exposure PK trial found statistically significantly lower AUC’s in men compared to women. Similar sex-based

differences were also observed irrespective of the route of metoclopramide administration (nasal, oral and IV) in one of our previous healthy volunteer studies.

In the most recent comparative exposure PK trial, results for women independently met equivalence criteria for $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ at the Gimoti dose proposed in the NDA. We submitted the NDA for a female-only indication based on a dose in women with equivalent exposure to the Listed Drug, Reglan Tablets 10 mg. and submitted supporting efficacy and safety data from our Phase 2b and Phase 3 trials at doses similar or lower than the dose proposed in the NDA.

Phase 3 Clinical Trial

In July 2016, we announced results from a Phase 3 clinical trial of Gimoti in female patients with symptoms associated with acute and recurrent diabetic gastroparesis. This U.S.-based, multicenter, randomized, double-blind, placebo-controlled, parallel group clinical trial evaluated the efficacy, safety and population PK of Gimoti in adult female patients with symptomatic diabetic gastroparesis and delayed gastric emptying by GES. Subjects received either Gimoti or placebo four times daily for 28 days. The primary endpoint was the change in symptoms from the baseline period to Week 4 as measured using a proprietary PRO instrument. On a daily basis, subjects reported the frequency and severity of their gastroparesis signs and symptoms using a telephone diary. The subjects' daily symptom scores were the basis for calculating their weekly scores using the PRO instrument.

A total of 205 women (mean age 52.7 years, 88% with type 2 diabetes; 79% postmenopausal, 51% using insulin, mean duration of diabetes 12.9 years, mean baseline glycosylated hemoglobin (HbA1c) 7.5%) were randomized and 93% completed the study. The primary endpoint for the ITT population was not statistically significant (p=0.881); however, in exploratory analyses, a treatment effect was seen at Weeks 1 to 3 for patients with higher baseline symptom scores (moderate to severe) in the ITT population (n=105) and for all four weeks for the per protocol population (see Table 1 below). There were also clinically and statistically significant improvements in nausea and abdominal pain, which are two of the more severe and debilitating symptoms of gastroparesis (see Table 2 below).

In July 2015, FDA issued a draft guidance document regarding the clinical evaluation of drugs for the treatment of gastroparesis, in which FDA states that in order to optimize the ability to demonstrate a treatment effect, clinical trials in this indication should enroll patients with higher symptom severity (moderate to severe). The improvements observed in our exploratory analyses of our Phase 3 study focused on this subset of patients enrolled in the study. At the time this draft guidance was issued, our Phase 3 study, designed to include patients with a range of symptom severity, had been actively enrolling for more than a year. The overall efficacy results were not significant, due in large part to the patients with less severe symptoms who responded to placebo. Importantly, patients with more severe symptoms experienced a statistically-significant treatment effect with Gimoti, consistent with the recommendation in the draft guidance on clinical studies of gastroparesis.

Reports of treatment-emergent adverse events were similar in both groups (36% Gimoti and 35% placebo) and most were mild or moderate in severity. There were slightly more reports of nasal irritation in subjects receiving placebo than in subjects receiving Gimoti. In particular, there were no adverse events of special interest, such as the central nervous system effects observed (see Table 3 below).

These safety results were consistent with findings from previous Gimoti studies that showed the nasal formulation of metoclopramide has a favorable safety profile and is well-tolerated by healthy volunteers and patients with diabetic gastroparesis. There have been no reports of tardive dyskinesia among the more than 1,400 exposed healthy volunteers and patients over the metoclopramide nasal spray clinical development program.

Table 1: Phase 3 Change from Baseline in Daily Total Symptom Scores by Week in Analysis Populations with Moderate to Severe Symptoms at Baseline

Population	Time Period	Placebo[1]	Gimoti[1]	p-value[2]
		(N = 53)	(N = 52)	
	Week 1	-0.387	-0.588	0.036
	Week 2	-0.614	-0.950	0.025
	Week 3	-0.749	-1.096	0.039
Intent-to-Treat	Week 4	-0.856	-1.220	0.085*
		(N = 40)	(N = 38)	
	Week 1	-0.362	-0.623	0.019
	Week 2	-0.625	-1.040	0.015
	Week 3	-0.714	-1.286	0.003
Per Protocol	Week 4	-0.841	-1.373	0.014

Table 2: Phase 3 Change from Baseline in Daily Nausea and Upper Abdominal Pain Scores by Week in Intent to Treat Population with Moderate to Severe Symptoms at Baseline

Symptom	Time Period	Placebo[1] (N = 53)	Gimoti[1] (N = 52)	p-value[2]
Nausea	Week 1	-0.370	-0.859	0.001
	Week 2	-0.696	-1.149	0.032*
	Week 3	-0.818	-1.242	0.043
	Week 4	-0.905	-1.404	0.027
Upper Abdominal Pain	Week 1	-0.394	-0.641	0.025
	Week 2	-0.554	-0.990	0.016
	Week 3	-0.690	-1.194	0.008
	Week 4	-0.791	-1.218	0.047

[1] LSMean from analysis of covariance, or ANCOVA

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[2] p-value is obtained from an ANCOVA model with fixed effect for treatment group and the baseline value as a covariate. If the normality assumption was not met, the p-value was obtained from a rank ANCOVA test and denoted with an *.

Table 3: Selected Treatment-Emergent Adverse Events Reported by More than 2 Subjects in Any Treatment Group

Adverse Event	Placebo (N = 103)	Gimoti (N = 102)
Headache	7 (7%)	5 (5%)
Nasal discomfort	4 (4%)	1 (1%)
Epistaxis	2 (2%)	1 (1%)
Fatigue	1 (1%)	2 (2%)

In December 2016, we announced the completion of a second pre-NDA meeting with FDA. The purpose of the meeting was to discuss efficacy and safety results from the Phase 3 clinical trial and submission strategies for an NDA. At the pre-NDA meeting FDA agreed that a comparative exposure PK trial was acceptable as a basis for submission of a Gimoti NDA. The comparative exposure PK trial will serve as a portion of the full 505(b)(2) data package to include prior efficacy and safety data developed by us and FDA's prior findings of safety and efficacy for the Listed Drug, Reglan Tablets 10 mg.

In the first pre-NDA meeting with FDA held in August 2016, we confirmed various regulatory, CMC, and non-clinical requirements for our potential NDA submission. In February 2017, we announced that we received a letter from FDA exempting Gimoti from HG Validation study requirements prior to submission of the NDA.

Male Companion Trial

We also conducted a companion clinical trial with Gimoti in male patients with symptoms associated with acute and recurrent diabetic gastroparesis to assess the safety and efficacy of Gimoti in men. This trial was requested by FDA to confirm the Phase 2b trial results and to capture additional safety data in men. The design of the male study was the same as the study in women and was initiated in April 2014 at sites also enrolling the Phase 3 study in women. Given that diabetic gastroparesis is predominately a female disorder, enrollment was challenging and the trial spontaneously stopped enrolling with 53 randomized male subjects (26 on Gimoti).

In November 2016, the data from the study were analyzed and futility was demonstrated. Results confirmed that even if the trial had fully enrolled, the results would not have differed. As we anticipated at the beginning of the trial, based on the prior Phase 2b data, the results of the trial showed no statistically significant efficacy in men. The safety profile for Gimoti was well-tolerated and the safety profile was comparable to placebo. The male trial was not required for submission of the Gimoti NDA for women; however, we included safety data from this study in the NDA submission.

Phase 2b Clinical Trial

We have evaluated Gimoti in a multicenter, randomized, double-blind, placebo-controlled parallel group, dose-ranging Phase 2b clinical trial in 287 subjects (71% female) with diabetic gastroparesis. Subjects in the trial were between the ages of 18 and 75, with a history of diabetes (type 1 and type 2) and diabetic gastroparesis, who had a baseline modified Gastroparesis Cardinal Symptom Index Daily Diary, or mGCSI-DD, of >2 and <4 for the seven days prior to randomization to blinded study drug (Gimoti or placebo).

In the pre-specified analysis of the primary endpoint, mean mGCSI-DD total score change from Baseline to Week 4, by gender, there was a benefit demonstrated in female subjects that was clinically and statistically significant ($p<0.025$) while male subjects demonstrated a high placebo response rate. This improvement in mGCSI-DD was

supported by secondary and exploratory measures of efficacy in females across the majority of parameters evaluated. Due to the results in men, the primary objective of statistical significance in the overall population was not achieved (p=0.15).

We believe this Phase 2b trial is the largest ever conducted in a diabetic gastroparesis population for any approved metoclopramide dosage forms (oral tablet, orally disintegrating tablet and injection). Previous metoclopramide studies enrolled small numbers of subjects and did not evaluate treatment effects by gender. For example, fewer than 130 gastroparesis subjects were enrolled across all studies included in the NDA for the Listed Drug, Reglan Tablets 10 mg., a branded form of metoclopramide currently marketed in the United States by Ani Pharmaceuticals.

The results of our Phase 2b trial are consistent with what is known about the gender effects in other GI motility disorders. GI motility and functional GI disorders, including gastroparesis, are more common in females than in males. Also, healthy females generally have slower gastric emptying rates. In a study conducted at Temple University (Parkman, et al), gastric emptying of solid food in normal young women was shown to be slower than in age-matched men, even in the first 10 days of the menstrual cycle when estrogen and progesterone levels are low, and the delay in gastric emptying of solids in women appears to be primarily due to altered distal gastric motor function. One explanation may be that less vigorous antral contractions may contribute to slower breakdown of food particles and thus delay the rate of emptying.

Gastrointestinal disorders present differently in males and females and responses to therapy vary by gender. There is general consensus among thought leaders in GI motility that women have a higher prevalence of symptoms, their neural and sensory pathways differ, and hormones, such as estrogen and progesterone, play a role. While the Gimoti Phase 2b trial is the first report of a gender- based difference in response to metoclopramide among subjects with diabetic gastroparesis, gender effects have been reported in drug studies for other GI disorders, such as IBS. For example, products such as Lotronex® (alosetron), Zelnorm® (tegaserod) and Amitiza® (lubiprostone) were approved by FDA based on effectiveness in women, but not in men.

Phase 2b Trial Design

The Phase 2b clinical trial consisted of up to a 23-day screening period and a seven-day washout period, followed by 28 days of treatment with study drug. We evaluated two dosage strengths of Gimoti: 10 mg and 14 mg; as well as placebo. The study drug was administered for the 28-day treatment period as a single nasal spray four times daily, 30 minutes before meals and at bedtime. Subjects recorded the severity of their gastroparesis symptoms in a telephonic diary using an interactive voice response system once each day. The symptoms were analyzed using a patient reported outcomes instrument, the Gastroparesis Cardinal Symptom Index Daily Diary, or GCSI-DD, developed for collecting and analyzing data to evaluate the effectiveness of treatments for gastroparesis.

The GCSI-DD contains nine signs and symptoms (nausea, retching, vomiting, stomach fullness, not able to finish a normal sized meal, feeling excessively full after meal, loss of appetite, bloating, and stomach or belly visibly larger) grouped in three subscales. The daily score is calculated as a mean of three subscale means. Additional signs and symptoms collected in the daily diary included abdominal pain, abdominal discomfort, number of hours of nausea, number of episodes of vomiting, and overall severity of gastroparesis symptoms. In close collaboration with the staff of FDA's Division of Gastroenterology and Inborn Errors Products and the Clinical Outcome Assessments, or COA, these additional symptom data were used to further refine the patient reported outcome instrument.

The result is the mGCSI-DD comprised of four symptoms (nausea, early satiety, bloating, and upper abdominal pain) rated from zero (none) to five (very severe). The instrument has been optimized to detect symptom variability on a severity continuum from nausea to vomiting.

Phase 2b Efficacy Results

Two patient reported outcome endpoints (mGCSI-DD and GCSI-DD) were examined in ITT population based on the protocol design and FDA communications:

- The primary efficacy endpoint was the change from seven-day baseline to Week 4 of the treatment period in the mGCSI-DD total score (mean of four symptoms).
- The second efficacy endpoint analyzed was the change from seven-day baseline to Week 4 of the treatment period in the GCSI-DD total score (mean of three subset means with a total of nine symptoms).

Although an overall improvement in symptoms was observed in Gimoti-treated subjects with diabetic gastroparesis compared to placebo, the difference was not statistically significant due to a high placebo response among male subjects. However, statistically significant improvement in gastroparesis symptoms was observed in female subjects

with diabetic gastroparesis as measured by the mGCSI-DD and GCSI-DD total scores for both doses of Gimoti compared to the placebo. The beneficial effect of treatment in females appears to be uniform. The results are consistent across the overall endpoints, the individual components, and the two dose groups.

The observed differences in efficacy were based on gender and were not due to severity of baseline disease or other demographic characteristics. No statistically significant differences were observed in efficacy between the 10 mg and 14 mg Gimoti doses; thus the 10 mg dose was considered the lowest effective dose in this study. The table below summarizes the p-values observed for both doses of Gimoti compared to placebo in the Phase 2b clinical trial across all subjects and for male and female subjects separately.

Gimoti Phase 2b Clinical Trial

Gastroparesis Study Endpoint Points P-Value Summary

(Gimoti vs. Placebo: Change from Baseline to Week 4)

	Gimoti 10 mg p-values	Gimoti 14 mg p-values
mGCSI-DD Total Score (per FDA guidance) (1)		
All Subjects	0.1504	0.3005
Females	0.0247	0.0215
Males	0.4497	0.2174
GCSI-DD Total Score (per trial protocol) (2)		
All Subjects	0.2277	0.5266
Females	0.0485	0.0437
Males	0.4054	0.0972

P-values for pairwise comparisons are obtained from an ANCOVA model with effects for treatment group and Baseline value as a covariate.

(1) The mGCSI-DD was comprised of four symptoms collected on a severity rating scale of 0 to 5. Baseline was seven days prior to treatment or qualifying days during washout and Week 4 was days 21 to 27 of treatment.

(2) The GCSI-DD was comprised of nine symptoms collected on a severity rating scale of 0 to 5. Baseline was seven days prior to treatment or qualifying days during washout and Week 4 was days 21 to 27 of treatment.

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The table below summarizes the key data from the trial across all subjects and for female and male subjects separately:

Gimoti Phase 2b Clinical Trial

Primary Endpoint: Mean mGCSI-DD Total Score Change

from Baseline to Week 4 by All Subjects and Gender

(intent-to-treat, last observation carried forward on treatment)

Time Point	Placebo (N=95)	Metoclopramide 10 mg IN (N=96)	Metoclopramide 14 mg IN (N=96)
ALL SUBJECTS			
Baseline (1)			
N	95	96	96
Mean (SD)	2.8 (0.57)	2.9 (0.60)	2.8 (0.62)
Week 4			
N	95	96	96
Mean (SD)	1.8 (1.00)	1.6 (1.06)	1.7 (0.90)
Change from Baseline to Week 4			
N	95	96	96
Mean (SD)	- 1.0 (0.89)	-1.2 (1.18)	-1.2 (0.94)
Difference of Least Square Means (95% CI)		-0.20 (-0.47, 0.07)	-0.14 (-0.42, 0.13)
Pairwise p-value vs. Placebo (2)		0.1504	0.3005
Difference of Least Square Means (95% CI)			0.06(-0.22, 0.33)
Pairwise p-value vs. Metoclopramide 10 mg (2)			0.6830
FEMALES			
Baseline (1)			
N	68	65	70
Mean (SD)	2.7 (0.54)	2.9 (0.62)	2.9 (0.62)
Week 4			
N	68	65	70
Mean (SD)	1.9 (1.02)	1.6 (1.08)	1.7(0.94)
Change from Baseline to Week 4			
N	68	65	70
Mean (SD)	- 0.8 (0.79)	-1.2 (1.18)	-1.3(0.98)
Difference of Least Square Means (95% CI)		-0.38 (-0.71, -0.05)	-0.38 (-0.71, -0.06)
Pairwise p-value vs. Placebo (2)		0.0247	0.0215
Difference of Least Square Means (95% CI)			-0.00 (-0.33, 0.32)
Pairwise p-value vs. Metoclopramide 10 mg (2)			0.9864
MALES			
Baseline (1)			
N	27	31	26
Mean (SD)	2.9 (0.63)	2.8(0.54)	2.5 (0.56)
Week 4			
N	27	31	26
Mean (SD)	1.4 (0.84)	1.6(1.05)	1.7 (0.79)

Change from Baseline to Week 4			
N	27	31	26
Mean (SD)	- 1.4 (0.98)	-1.2 (1.21)	-0.9 (0.78)
Difference of Least Square Means (95% CI)		0.18 (-0.30, 0.66)	0.32 (-0.19, 0.83)
Pairwise p-value vs. Placebo (2)		0.4497	0.2174
Difference of Least Square Means (95% CI)			0.14 (-0.35, 0.63)
Pairwise p-value vs. Metoclopramide 10 mg (2)			0.5805

(1) Baseline is defined as the mean mGCSI-DD total score during the washout period
(2) p-values for pairwise comparisons are obtained from an ANCOVA model with effects for treatment group and baseline value as a covariate

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Phase 2b Safety Observations

In the Phase 2b clinical trial, Gimoti 10 mg and 14 mg doses were well-tolerated and no differences in the safety profiles were observed between the two doses administered. No serious adverse events occurred related to study treatment. In addition, there were no clinically-meaningful differences observed in clinical laboratory parameters, physical examination findings, or electrocardiogram recordings.

Adverse events that occurred more commonly in both Gimoti 10 mg and 14 mg doses compared to placebo (≥2% difference between treated compared to placebo groups) were dysgeusia, headache, nasal discomfort, rhinorrhea, throat irritation, fatigue, hypoglycemia and hyperglycemia. The majority of adverse events were mild to moderate and transient in nature.

Treatment-Emergent Adverse Events Reported by More than Two Subjects in Any Treatment Group

	All Subjects		
System Organ Class Preferred Term	Placebo (N = 95)	Gimoti 10 mg (N = 95)	Gimoti 14 mg (N = 95)
Nervous System Disorders			
Dysgeusia	4 (4.2%)	12 (12.6%)	13 (13.7%)
Headache	4 (4.2%)	7 (7.4%)	8 (8.4%)
Dizziness	2 (2.1%)	3 (3.2%)	3 (3.2%)
Gastrointestinal Disorders			
Diarrhea	9 (9.5%)	3 (3.2%)	2 (2.1%)
Nausea	4 (4.2%)	1 (1.1%)	4 (4.2%)
Gastroesophageal reflux disease	1 (1.1%)	4 (4.2%)	0 (0.0%)
Respiratory, Thoracic, and Mediastinal Disorders			
Epistaxis	2 (2.1%)	2 (2.1%)	3 (3.2%)
Cough	2 (2.1%)	0 (0.0%)	3 (3.2%)
Nasal discomfort	0 (0.0%)	3 (3.2%)	2 (2.1%)
Rhinorrhea	1 (1.1%)	1 (1.1%)	3 (3.2%)
Throat irritation	1 (1.1%)	0 (0.0%)	3 (3.2%)
Infections and Infestations			
Upper respiratory tract infection	4 (4.2%)	0 (0.0%)	2 (2.1%)
Nasopharyngitis	1 (1.1%)	3 (3.2%)	1 (1.1%)
General Disorders and Admin Site Conditions			
Fatigue	1 (1.1%)	5 (5.3%)	6 (6.3%)
Metabolism & Nutrition Disorders			
Hyperglycemia	1 (1.1%)	1 (1.1%)	3 (3.2%)
Hypoglycemia	1 (1.1%)	1 (1.1%)	3 (3.2%)
Psychiatric Disorders			
Depression	3 (3.2%)	0 (0.0%)	0 (0.0%)

Phase 1 Comparative Bioavailability Bridging Study

Our Phase 1 clinical trial of Gimoti was an open-label, four-treatment, four-period, four-sequence crossover study conducted at a single study center. Forty healthy volunteers were enrolled and randomly assigned to one of four treatment sequences. After an overnight fast, subjects received a single dose of each of the metoclopramide treatments (10 mg Gimoti, 20 mg Gimoti, 10 mg Reglan tablet, and 5 mg/mL Reglan injection) in random sequence with a seven-day washout period between doses. Thirty-nine subjects received at least one dose of metoclopramide. The pharmacokinetic analysis population consisted of 37 subjects who received all four treatments and two subjects who

received three of the four treatments.

After nasal spray administration of the 10 mg and 20 mg doses of Gimoti, mean plasma metoclopramide concentrations increased in a dose-related manner, as did mean values for C_{max} and AUC_{inf}. The absolute bioavailability of Gimoti after nasal spray administration was comparable for the 10 mg (47.4%) and 20 mg (52.5%) doses as were the bioavailabilities relative to the oral tablet (60.1% and 66.5%, respectively).

The graphs below illustrate the mean plasma concentrations of the active ingredient in the two doses of Gimoti as well as the oral and injection forms.

Thorough ECG (QT/QTc) Study

We conducted a randomized, double-blind, double-dummy, four-way crossover thorough ECG (QT/QTc) study of Gimoti in 2014. The study was designed in accordance with FDA's published guidance on clinical evaluation of QT/QTc interval, and compared the effects of Gimoti on the QT/QTc interval when administered at therapeutic and supratherapeutic doses in 48 healthy female and male volunteers. Moxifloxacin, an antibiotic known to prolong the QT/QTc interval, was used as the positive control.

In December 2014, we reported that data from the study met the pre-specified primary endpoint, demonstrating that Gimoti, at therapeutic and supratherapeutic doses, did not prolong the QT/QTc interval in healthy subjects. The study was conducted to satisfy a safety requirement by FDA in support of our submission of an NDA for Gimoti.

In 2014, we also completed a thorough ECG (QT/QTc) study and reported positive results. Prolongation of the QT interval may increase the risk for cardiac arrhythmias. Data from the thorough ECG (QT/QTc) trial met the pre-specified primary endpoint, demonstrating that Gimoti, at therapeutic and supratherapeutic doses, did not prolong the QT/QTc interval in healthy subjects.

Prior Development

From 1985 to present, we, or our predecessors, have conducted numerous clinical studies to evaluate the safety and pharmacokinetic profile of nasal spray formulations of metoclopramide in healthy volunteers and the safety, efficacy, and pharmacokinetic profile of metoclopramide nasal spray in patients. More than 1,400 subjects have been exposed to nasal formulations of metoclopramide at doses ranging from 10 mg to 80 mg in these studies.

In one study, a Phase 2A, multicenter, randomized, open-label, parallel design study, Questcor Pharmaceuticals, Inc., or Questcor (now part of Mallinckrodt, plc), compared the efficacy and safety of two doses of metoclopramide nasal spray, 10 mg and 20 mg, with FDA-approved 10 mg metoclopramide tablet. For the primary efficacy endpoint in the per protocol population analysis, a statistically significant difference in the total symptom score between baseline and week 6 for both the nasal 10 mg ($p=0.026$) and nasal 20 mg ($p=0.008$) cohorts compared to the oral 10 mg group was observed. Metoclopramide nasal spray was initially developed by Nastech Pharmaceutical Company, Inc. in precursor formulations to Gimoti and subsequently acquired and developed by Questcor.

We acquired rights to this product candidate from Questcor in 2007. We then optimized the acquired formulation of metoclopramide nasal spray to improve stability and remove inactive ingredients to improve the palatability and tolerability of Gimoti for subjects. We also developed the current formulation with excipients that are at or below the levels listed in FDA's Inactive Ingredient Database for nasal products.

We evaluated the current formulation of Gimoti with the same nasal spray pump in six completed clinical trials enrolling a total of 746 healthy volunteers and patients with diabetic gastroparesis. Phase 1 (39 and 108), thorough ECG (54), Phase 2 (287), Phase 3 (205) and Companion (53).

The primary container closure system for Gimoti is comprised of an amber glass vial directly attached to a pre-assembled spray pump unit with a protection cap. Each multi dose sprayer system comes preassembled and capable of delivering a 30-day supply (120 doses at 4 doses per day.) The sprayer is a standardized metered sprayer technology utilized in other nasal spray products as well as the amber vial.

Intellectual Property and Proprietary Rights

Overview

We are building an intellectual property portfolio for Gimoti in the United States and abroad. We seek patent protection in the United States and internationally for our product candidate, its methods of use and processes for its manufacture, and for other technologies, where appropriate. Our policy is to actively seek to protect our proprietary position by, among other things, filing patent applications in the United States and abroad relating to proprietary technologies that are important to the development of our business. We also rely on trade secrets, know-how, continuing technological innovation and in-licensing opportunities to develop and maintain our proprietary position. We cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our technology.

Our business success will depend significantly on our ability to:

- secure, maintain and enforce patent and other proprietary protection for our core technologies, inventions and know-how;
- obtain and maintain licenses to key third-party intellectual property owned by such third parties;
- preserve the confidentiality of our trade secrets; and
    - operate without infringing upon valid, enforceable third-party patents and other rights.

Patent Portfolio

Our patent portfolio includes the following U.S. patents and patent applications as of February 28, 2019:

- U.S. Patent 6,770,262—Nasal Administration of Agents for the Treatment of Gastroparesis. This patent is expected to expire in 2021.
- U.S. Patent 8,334,281—Nasal Formulations of Metoclopramide. This patent is expected to expire in 2030 and has a pending Continuation application (U.S. Non-Provisional Patent Application No. 16/181,841).
- U.S. Non-Provisional Patent Application No. 16/016,246 —Treatment of Symptoms Associated with Female Gastroparesis. If granted, this patent would be expected to expire in 2032.

We have also been granted European and Canadian patents for the method of use of metoclopramide via nasal delivery for gastroparesis. These patents are expected to expire in 2021. We have also been granted European and Canadian patents for pharmaceutical compositions comprising metoclopramide. These patents are expected to expire in 2030. Additional patent applications have been filed in the United States and abroad related to more recent clinical trial findings.

Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidate are obtained, once the patent life has expired, we may be open to competition from competitive products, including generics. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

Other Intellectual Property Rights

We currently have a registered trademark for EVOKE PHARMA and a trademarked product name for GIMOTI in the United States.

Confidential Information and Inventions Assignment Agreements

We require our employees and consultants to execute confidentiality agreements upon the commencement of employment, consulting or collaborative relationships with us. These agreements provide that all confidential information developed or made known during the course of the relationship with us be kept confidential and not disclosed to third parties except in specific circumstances.

In the case of employees, the agreements provide that all inventions resulting from work performed for us, utilizing our property or relating to our business and conceived or completed by the individual during employment shall be our exclusive property to the extent permitted by applicable law. Our consulting agreements also provide for assignment to us of any intellectual property resulting from services performed for us.

Sales and Marketing

We plan to commercialize Gimoti in the United States alone, or in partnership with pharmaceutical companies that have established development and sales and marketing capabilities. Our strategy for Gimoti, if approved by FDA, will be to establish Gimoti as the prescription product of choice for diabetic gastroparesis in women. If the product candidate is approved, our expectation is that Gimoti would initially be marketed to gastrointestinal and internal medicine specialists, primary care physicians and select health care providers. We have engaged NGP to manage the commercial operations for a dedicated sales team to market Gimoti. We anticipate engaging a third-party sales organization to retain, train and deploy this direct sales force or, if we are unable to reach an agreement with a third party on acceptable terms, hire a sales force directly.

Commercial Services Agreement with Novos Growth, LLC

On January 5, 2019, we entered into the NGP Agreement with NGP for the commercialization of Gimoti. Pursuant to the NGP Agreement, NGP will manage the commercial operations for a dedicated sales team to market Gimoti, if approved by FDA, to gastroenterologists and other targeted health care providers.

Under the terms of the NGP Agreement, we maintain ownership of the Gimoti NDA, as well as legal, regulatory, and manufacturing responsibilities for Gimoti. We will also retain a contract sales organization, which would be managed by NGP. We will record sales for Gimoti and retain more than 80% of product profits. NGP will receive a percentage of product profits in the mid-to-high teens as a service fee. Product profits are the net sales (as defined in the NGP Agreement) of Gimoti, less the costs of goods sold, specified commercialization costs and the interest to be paid on the NGP Working Capital Loan, as described below (such product profit amount, the “Contribution Profits”). During the term of the NGP Agreement, NGP agreed to not commercialize a competing product in the United States other than pursuant to the NGP Agreement.

Pursuant to the NGP Agreement, NGP has agreed to finance our working capital requirements for specified commercialization costs (including costs related to marketing, sales and patient assistance programs) in an amount by which Contribution Profits are expected to fall (or do actually fall) below zero (as projected by sales forecasts and a commercialization budget) to be drawn by us on a monthly basis, as needed, or the NGP Working Capital Loan, pursuant to a credit agreement to be negotiated in good faith by us and NGP, or the NGP Credit Agreement. The NGP Working Capital Loan will be repaid by us, if at all, only out of positive Contribution Profits, unless the NGP Agreement is terminated (a) by NGP due to a material breach by us, or (b) by us other than due to the gross negligence or intentional misconduct of NGP. Termination of the NGP Agreement by NGP for any other reason (including, without limitation, minimum net sales thresholds and negative Contribution Profits, as described below) will cause the NGP Working Capital Loan to be forgiven in full. The interest rate and other terms of the NGP Working Capital Loan will be set forth in the NGP Credit Agreement.

In addition, under the NGP Agreement, NGP has agreed to provide a line of credit of up to $5.0 million to us following NDA approval of Gimoti, if any, and for a period of up to nine months thereafter. The line of credit will be extended pursuant to a credit agreement to be negotiated in good faith by the parties. NGP will receive a low single digit percentage on net sales of Gimoti in lieu of any interest on the line of credit, or the NGP Credit Fee; provided that in no event shall the cumulative NGP Credit Fee exceed twice the amount of the principal borrowed by us under the line of credit. The line of credit will mature on the earlier of 30 days following the date the NGP Credit Fee is twice the amount of the borrowed principal and the two-year anniversary of the date the principal is borrowed by us. In the event we secure financing from a third-party wholesale distributor for the purchase of Gimoti for launch in excess of $2.5 million dollars, NGP will no longer be required to offer the line of credit.

The term of the NGP Agreement is five years from the date of commercial launch of Gimoti, if any, after which we will recapture 100% of product sales and assume all corresponding responsibilities. Within 30 days after each one-year anniversary of the NGP Agreement, either party may terminate the NGP Agreement if net sales of Gimoti do not meet certain annual thresholds. Either party may terminate the NGP Agreement for the material breach of the other party, subject to a 60-day cure period, or in the event an insolvency petition of the other party is pending for more than 60 days. Either party may also terminate the NGP Agreement upon 30-days written notice to the other party if Gimoti is subject to a safety recall, the parties are unable to agree to a commercialization plan and budget by a specified date, or if the Contribution Profit is negative for any calendar quarter beginning with the first full calendar quarter nine

months following commercial launch. In addition, NGP may terminate the NGP Agreement if Gimoti is not approved by FDA by April 30, 2019, if we withdraw Gimoti from the market for more than 180 days, or if we are unable to provide product samples for use by the salesforce in a timely manner. We may also terminate the NGP Agreement if we undergo a change of control, subject to a one-time payment equal to between four times and one times annualized service fees paid by us under the NGP Agreement, with such amount based on which year (between one and five years) after commercial launch the change of control occurs, provided if the change of control occurs within one year of commercial launch, such amount will be the greater of the specified annualized service fee amount and $5 million.

Manufacturing

We do not own or operate manufacturing facilities for the production of Gimoti, nor do we have plans to develop our own manufacturing operations in the foreseeable future. We currently depend on third-party contract manufacturers for all of our required raw materials, drug substance and finished product for our product development and clinical trials. We currently use a third-party consultant, which we engage on an as-needed, hourly basis, to manage product development and manufacturing contractors.

In April 2015, we announced the completion of production of a commercial scale lot of Gimoti as required by FDA. With the completion of this large-scale production of Gimoti, we believe we have demonstrated our ability to manufacture Gimoti at commercial scale quantities in accordance with CMC. In addition to data from this recent program, we have a three-year registration stability data package from previous studies which have all met proposed specifications. These CMC datasets were submitted as part of the NDA submission.

In November 2017, we entered into a Manufacturing Services Agreement with Patheon UK Limited, or Patheon, a wholly-owned subsidiary of Thermo Fisher, Inc., pursuant to which Patheon has agreed to manufacture commercial quantities of Gimoti. Under the terms of the agreement, we are required to purchase a certain percentage of our requirements for our Gimoti product intended for commercial sale, provided certain terms and conditions are met. The initial term of the agreement commenced in November 2017 and will continue in effect until December 31st of the year that is five years from the date Gimoti first receives approval for marketing from FDA or any other foreign regulatory agencies competent to grant marketing approvals for pharmaceutical products. This initial term shall be automatically renewed for additional one-year terms, unless either party provides written notice of its intention to terminate the agreement upon notice within a specified time prior to the end of the then current term. Either party may terminate the agreement effective immediately upon written notice to the other in the event that (i) the other party dissolves, is declared insolvent or bankrupt by a court of competent jurisdiction, (ii) a voluntary petition of bankruptcy is filed in any court of competent jurisdiction, or (iii) the agreement is assigned for the benefit of creditors. We may terminate the agreement upon specified prior written notice if any governmental or regulatory authority, including, but not limited to, FDA, takes any action, or raises any objection, that prevents us from importing, exporting, purchasing, or selling Gimoti. Patheon or we may terminate the agreement upon specified prior written notice to the other party if Patheon or we, as applicable, assigns any of our rights under the agreement to an assignee that is (i) not a credit worthy substitute for the assigning party; or (ii) a competitor of assigning party. Moreover, either party may terminate the agreement upon written notice to the other party where the other party has failed to remedy a material breach of any of its representations, warranties, or other obligations under the agreement within a specified period of time following receipt of a written notice of the breach, subject to specified terms and conditions.

In May 2016, we entered into a Master Supply Agreement with Cosma S.p.A., or Cosma, pursuant to which Cosma will be the exclusive commercial supplier of metoclopramide for the manufacture of Gimoti. Under the supply agreement, Cosma will supply metoclopramide pursuant to purchase orders which we may deliver to Cosma from time to time, and there is no minimum supply requirement. In the event Cosma discontinues supply of metoclopramide for any reason, including by reason of a force majeure event, or materially changes the metoclopramide specifications, then we may require Cosma to supply up to a two years' supply of the metoclopramide based on our purchase orders over the preceding two years. The term of the supply agreement is three years, which term shall be automatically extended (1) for an additional period equivalent to the time elapsing from May 2016 to the

date of the first commercial launch of Gimoti and (2) for successive one-year periods thereafter, unless terminated earlier. Either party may terminate the supply agreement on 180 days' written notice to the other party or on a 30 days' written notice to the other party for such party's material uncured breach.

Competition

The pharmaceutical industry is characterized by intense competition and rapid innovation. Our potential competitors include large pharmaceutical and biotechnology companies, specialty pharmaceutical and generic drug companies, academic institutions, government agencies and research institutions. We believe the key competitive factors that will affect the development and commercial success of our product candidates are efficacy, safety and tolerability profile, reliability, convenience of dosing, coverage pricing and reimbursement.

Many of our potential competitors have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of products and the commercialization of those products. Accordingly, our competitors may be more successful than we may be in obtaining FDA approval for drugs and achieving widespread market acceptance. Our competitors' drugs may be more effective, or more effectively marketed and sold, than any drug we may commercialize and may render our product candidates obsolete or non-competitive before we can recover the expenses of developing and commercializing any of our product candidates. We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available. Finally, the development of new treatment methods for the diseases we are targeting could render our drugs non-competitive or obsolete.

We expect that, if approved, Gimoti will compete directly with metoclopramide oral, erythromycin and domperidone as a treatment for gastroparesis. Metoclopramide is the only product currently approved in the United States to treat gastroparesis. Metoclopramide is available from a number of generic pharmaceutical manufacturers as well as in branded form in the United States under the tradename Reglan® Tablets from Ani Pharmaceuticals.

Salix Pharmaceuticals, Inc. launched an orally dissolving tablet formulation of metoclopramide in 2009. Other programs in the gastroparesis pipeline include new chemical entities in earlier-stage clinical trials. In addition to our Gimoti product candidate, we are aware of the following development candidates; all of which are in clinical development.

Gastroparesis Treatment Development Pipeline

Product	Class	Route	Company	Status
Gimoti	dopamine antagonist /mixed 5-HT3 antagonist 5-HT4 agonist	nasal	Evoke Pharma	NDA Submitted
Relamorelin/RM-131	ghrelin agonist	sub-cutaneous	Rhythm/Allergan	Phase 3
Velusetrag/TAK-954	5-HT4 receptor agonist	oral	Theravance/Takeda	Phase 2
Tradipitant	NK-1 antagonist	oral	Vanda	Phase 2
Renzapride	5-HT4 agonist/ 5-HT3 antagonist	oral	Endologic	Phase 2
NG-101	D2/D3 antagonist	Oral	Neurogastrx	Phase 1

Relamorelin, also called RM-131, is a small-peptide analog of ghrelin, a hormone produced in the stomach that stimulates gastrointestinal activity. The compound is being developed for GI motility disorders and has shown efficacy in surgical and opiate-induced ileus in animal models due to a direct prokinetic effect. In October 2016, a Phase 2b study failed to reach statistical significance. Following the trial results, Allergan plc. executed its option to acquire Rhythm Holding Company, LLC. Relamorelin reverses body weight loss in cachexia models.

Velusetrag, also called TAK-954, is a 5-HT4 receptor agonist compound under development for the treatment of gastroparesis by Takeda Pharmaceuticals in collaboration with Theravance Biopharma, Inc. In August 2018, Theravance announced that its Phase 2 study failed to reach statistical significance in the two higher doses tested, but did show statistical significance in the lower dose tested.

Tradipitant is a NK-1 antagonist that has been tested in various other indications by Vanda Pharmaceuticals Inc. In December 2018, a Phase 2 study reached statistical significance for the primary endpoint for treatment of nausea.

Renzapride, a 5-HT4 agonist and 5HT-3 antagonist, has been studied in more than 5,000 patients including one Phase 3 trial for the treatment of constipation-dominant irritable bowel syndrome (IBS-C). Renzapride demonstrated a small but statistically significant benefit in the Phase 3 study in IBS-C, however, the prior owner of the product decided to

not continue to pursue development of the drug for this indication. The drug was well tolerated and showed no evidence of cardiotoxicity. A pilot Phase 2 study in patients with diabetic gastroparesis showed that doses of 0.5 mg, 1.0 mg and 2.0 mg, once-daily, showed significant improvement in gastric emptying in a dose-dependent manner. This endpoint does not meet the July 2015 FDA guidance for gastroparesis recommending measurement of symptoms associated with gastroparesis.

Neurogastrx is currently developing NG-101. NG-101 is a selective and peripherally restricted dopamine D2/D3 receptor antagonist to treat gastroparesis. It is approved in countries outside the US in other indications.

One additional medication, Motilium (domperidone), a dopamine receptor modulator, is not FDA-approved, but is available in the United States through various compounding pharmacies under a specific FDA restricted-access program. The safety and efficacy of Motilium as a promotility agent is not fully established.

Technology Acquisition Agreement

In June 2007, we acquired all worldwide rights, data, patents and other related assets associated with Gimoti from Questcor pursuant to an asset purchase agreement. We paid Questcor $650,000 in the form of an upfront payment and $500,000 in May 2014 as a milestone payment based upon the initiation of the first patient dosing in our Phase 3 clinical trial for Gimoti. In August 2014, Mallinckrodt, plc, or Mallinckrodt, acquired Questcor. As a result of that acquisition, Questcor transferred its rights included in the asset purchase agreement with us to Mallinckrodt. In addition to the payments previously made to Questcor, we may be required to make additional milestone payments totaling up to $52 million. In March 2018, we amended the asset purchase agreement with Mallinckrodt to defer development and approval milestone payments, such that rather than paying two milestone payments based on FDA acceptance for review of the NDA and final product marketing approval, we would be required to make a single $5 million payment on the one-year anniversary after we receive FDA approval to market Gimoti.

The remaining $47 million in milestone payments depend on Gimoti's commercial success and will only apply if Gimoti receives regulatory approval. In addition, we will be required to pay to Mallinckrodt a low single digit royalty on net sales of Gimoti. Our obligation to pay such royalties will terminate upon the expiration of the last patent right covering Gimoti, which is expected to occur in 2032.

Government Regulation

FDA Review and Approval Process

In the United States, pharmaceutical products are subject to extensive regulation by FDA. The Federal Food, Drug, and Cosmetic Act, or FFDCA, and other federal and state statutes and regulations, govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling, and import and export of pharmaceutical products. Failure to comply with applicable FDA or other requirements may subject a company to a variety of administrative or judicial sanctions, such as FDA's refusal to approve pending applications, a clinical hold, warning letters, recall or seizure of products, partial or total suspension of production, withdrawal of the product from the market, injunctions, fines, civil penalties or criminal prosecution.

FDA approval is required before any new unapproved drug or dosage form, including a new use of a previously approved drug, can be marketed in the United States. The process required by FDA before a drug may be marketed in the United States generally involves:

- completion of pre-clinical laboratory and animal testing and formulation studies in compliance with FDA's good laboratory practice regulations;
- submission to FDA of an Investigational New Drug Application, or IND, for human clinical testing which must become effective before human clinical trials may begin in the United States;
- approval by an independent institutional review board, or IRB, at each clinical trial site before each trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practice, or GCP, regulations to establish the safety and efficacy of the proposed drug product for each intended use;
- satisfactory completion of an FDA pre-approval inspection of the facility or facilities at which the product is manufactured to assess compliance with FDA current good manufacturing practices, or cGMP, regulations, including, for devices and device components, the Quality System Regulation, or QSR, and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- submission to FDA of an NDA;
- satisfactory completion of an FDA advisory committee review, if applicable; and
- FDA review and approval of the NDA.

The pre-clinical and clinical testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all. Pre-clinical tests include laboratory evaluation of product chemistry, formulation, stability and toxicity, as well as animal studies to assess the characteristics and potential safety and efficacy of the product. The results of pre-clinical tests, together with manufacturing information, analytical data and a proposed clinical trial protocol and other information, are submitted as part of an IND to FDA. Some pre-clinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by FDA, unless FDA, within the 30-day time period, raises concerns or questions relating to one or more proposed clinical trials and places the clinical trial on a clinical hold, including concerns that human research subjects will be exposed to unreasonable health risks. In such a case, the IND sponsor and FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, our submission of an IND may not result in FDA authorization to commence a clinical trial. A separate submission to an existing IND must also be made for each successive clinical trial conducted during product development.

Further, an IRB covering each site proposing to conduct the clinical trial must review and approve the plan for any clinical trial and informed consent information for subjects before the trial commences at that site, and it must monitor the study until completed. FDA,

the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk or for failure to comply with the IRB's or regulatory requirements, or for other reasons, or FDA or IRB may impose other conditions.

Clinical trials involve the administration of the investigational new drug to human subjects 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. Sponsors of clinical trials generally must register and report, at the National Institutes of Health-maintained website ClinicalTrials.gov, key parameters of certain clinical trials. For purposes of an NDA submission and approval, human clinical trials are typically conducted in the following sequential phases, which may overlap or be combined:

- Phase 1: The drug is initially introduced into healthy human subjects or patients and tested for safety, dose tolerance, absorption, metabolism, distribution and excretion and, if possible, to gain an early indication of its effectiveness.
- 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 indications and to determine dose tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more extensive Phase 3 clinical trials.
- Phase 3: These are commonly referred to as pivotal studies. When Phase 2 evaluations demonstrate that a dose range of the product appears to be effective and has an acceptable safety profile, Phase 3 trials are undertaken in large patient populations to further evaluate dosage, to obtain additional evidence of clinical efficacy and safety in an expanded patient population at multiple, geographically-dispersed clinical trial sites, to establish the overall risk-benefit relationship of the drug and to provide adequate information for the labeling of the drug.
- Phase 4: In some cases, FDA may condition approval of an NDA for a product candidate on the sponsor's agreement to conduct additional clinical trials to further assess the drug's safety and effectiveness after NDA approval. Such post-approval trials are typically referred to as Phase 4 studies.

The results of product development, pre-clinical studies and clinical trials are submitted to FDA as part of an NDA. NDAs must also contain extensive information relating to the product's pharmacology, chemistry, manufacturing and controls, or CMC, and proposed labeling, among other things.

Under federal law, the submission of most NDAs is subject to a substantial application user fee, and the manufacturer and/or sponsor under an approved NDA are also subject to annual program fees. FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. FDA may request additional information rather than accept an NDA for filing. In this event, the NDA must be resubmitted with the additional information and is subject to payment of additional user fees. The resubmitted application is also subject to review before FDA accepts it for filing.

Once the submission has been accepted for filing, FDA begins an in-depth substantive review. Under PDUFA, FDA agrees to specific performance goals for NDA review time through a two-tiered classification system, Standard Review and Priority Review. Standard Review NDAs have a goal of being completed within ten months of the date of receipt by FDA (for drugs that do not contain new molecular entities) and ten months of the 60-day filing date (for drugs that contain new molecular entities). A Priority Review designation is given to drugs that treat a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The goal for completing a Priority Review is six months from the date of receipt by FDA (for drugs that do not contain new molecular entities) and six months of the 60-day filing date (for drugs that contain new molecular entities). However, FDA does not always complete its review within these timelines and the review can take substantially longer.

We submitted an NDA for Gimoti to FDA on June 1, 2018 and received a Day-74 communication letter in August 2018. The letter stated that the NDA was sufficiently complete to permit a substantive review and set a target goal date under PDUFA of April 1, 2019, reflecting Standard Review period for a product that does not contain a new chemical entity. On March 1, 2019, we received a DRL from FDA, which provided preliminary notice of certain deficiencies identified during FDA's initial review of the Gimoti NDA. Specifically, the DRL described concerns with

the information provided in the NDA, including concerns that insufficient evidence had been offered regarding product quality control and reproducibility specific to the commercially available sprayer device used with Gimoti, that there is a lack of adequate information to support sex-based efficacy claims and that the pharmacology data provided may not demonstrate bioavailability to the Listed Drug, Reglan Tablets 10 mg. Although a DRL reflects preliminary comments that are subject to change and does not reflect FDA's final decision on the NDA, approval of Gimoti by the PDUFA date of April 1, 2019, if any, is uncertain given the letter. We plan to respond to the deficiencies raised in the DRL to allow time for FDA to potentially complete its review prior to the PDUFA date. The review process may be extended to allow FDA to request and review additional information or obtain clarification regarding information provided in the original submission. FDA may refer applications for novel drug products or drug products which present difficult questions of safety or efficacy to an advisory committee for review, evaluation

and recommendation as to whether the application should be approved and under what conditions. FDA is not bound by the recommendation of an advisory committee, but it considers such recommendations carefully when making decisions.

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

After FDA evaluates the NDA and, in some cases, the related manufacturing facilities, it may issue an approval letter or a CRL to indicate that the review cycle for an application is complete or that the application is not ready for approval. CRLs generally outline the deficiencies in the submission and may require substantial additional testing or information in order for FDA to reconsider the application. Even with submission of this additional information, FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when the deficiencies have been addressed to FDA's satisfaction, FDA will typically issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

Once issued, FDA may withdraw product approval if ongoing regulatory requirements are not met or if safety problems are identified after the product reaches the market. In addition, FDA may require post-approval testing, including Phase 4 studies, and surveillance programs to monitor the effect of approved products which have been commercialized, and FDA has the power to prevent or limit further marketing of a product based on the results of these post-marketing programs. Drugs may be marketed only for the approved indications and in accordance with the provisions of the approved label, and, even if FDA approves a product, it may limit the approved indications for use for the product or impose other conditions, including labeling or distribution restrictions or other risk-management mechanisms. Further, if there are any modifications to the drug, including changes in indications, labeling, or manufacturing processes or facilities, we may be required to submit and obtain FDA approval of a new or supplemental NDA, which may require us to develop additional data or conduct additional pre-clinical studies and clinical trials.

Post-Approval Requirements

Once an NDA is approved, a product will be subject to pervasive and continuing regulation by FDA, including, among other things, requirements relating to drug/device listing, recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved products are required to register their establishments with FDA and state agencies, and are subject to periodic unannounced inspections by FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and generally require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon us and any third-party manufacturers that we 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, FDA may suspend, restrict or withdraw the approval, require a product recall, or impose additional restrictions or limitations 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, among other things:

- 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 FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product license 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.

FDA may require post-approval studies and clinical trials if FDA finds that scientific data, including information regarding related drugs, deem it appropriate. The purpose of such studies would be to assess a known serious risk or signals of serious risk related to the drug or to identify an unexpected serious risk when available data indicate the potential for a serious risk. FDA may also require a labeling change if it becomes aware of new safety information that it believes should be included in the labeling of a drug. Based on

feedback from FDA, we proposed a post-marketing safety trial as part of the Gimoti NDA submission. We expect to discuss the details of such a trial with FDA during the NDA review process.

The Food and Drug Administration Amendments Act of 2007 gave FDA the authority to require a Risk Evaluation and Mitigation Strategy, or REMS, from manufacturers to ensure that the benefits of a drug outweigh its risks. In determining whether a REMS is necessary, FDA must consider the size of the population likely to use the drug, the seriousness of the disease or condition to be treated, the expected benefit of the drug, the duration of treatment, the seriousness of known or potential adverse events, and whether the drug is a new molecular entity. If FDA determines a REMS is necessary, the drug sponsor must agree to the REMS plan at the time of approval. A REMS may be required to include various elements, such as a medication guide or patient package insert, a communication plan to educate health care providers of the drug's risks, limitations on who may prescribe or dispense the drug, or other measures that FDA deems necessary to assure the safe use of the drug. In addition, the REMS must include a timetable to assess the strategy at 18 months, three years, and seven years after the strategy's approval. FDA may also impose a REMS requirement on a drug already on the market if FDA determines, based on new safety information, that a REMS is necessary to ensure that the drug's benefits continue to outweigh its risks.

In March 2009, FDA informed drug manufacturers that it will require a REMS for metoclopramide drug products. FDA's authority to take this action is based on risk management and post market safety provisions within the Food and Drug Administration Amendments Act. The REMS consists of a Medication Guide, elements to assure safe use (including an education program for prescribers and materials for prescribers to educate patients), and a timetable for submission of assessments of at least six months, 12 months, and annually after the REMS is approved. In 2011, FDA determined that maintaining the Medication Guide as a part of the approved labeling is adequate to address the public health concern and meets the regulatory standards. We followed current labeling procedures and included a medication guide at the time of the NDA submission for Gimoti. Based on feedback from FDA, we proposed elements of a REMS to be included in the NDA submission. At this time the elements of the REMS for Gimoti are unclear as there are varying levels of requirements that may include a Medication Guide, similar to the Reglan Tablet, and other elements, such as a communication plan and an implementation plan, designed to ensure safe use, as well as a timetable for submission of post-marketing assessments after the REMS is approved.

FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market, and FDA imposes a number of complex regulations on entities that advertise and promote pharmaceuticals, which include, among others, standards for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities, and promotional activities involving the internet. While physicians may prescribe for off-label uses, manufacturers may only promote for the approved indications and in accordance with the provisions of the approved label. FDA and other agencies actively enforce the laws and regulations 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. Indeed, FDA has very broad enforcement authority under the FFDCA, and failure to abide by these regulations can result in penalties, including the issuance of a warning letter directing entities to correct deviations from FDA standards, a requirement that future advertising and promotional materials are pre-cleared by FDA, and state and federal civil and criminal investigations and prosecutions.

The distribution of prescription pharmaceutical products is also subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution, including a drug pedigree which tracks the distribution of prescription drugs.

Section 505(b)(2) New Drug Applications

As an alternate path to FDA approval for modifications to formulations or uses of products previously approved by FDA, an applicant may submit an NDA under Section 505(b)(2) of the FFDCA. Section 505(b)(2) was enacted as part

of the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Amendments, and permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. The applicant may rely upon published literature and FDA's findings of safety and effectiveness based on certain pre-clinical or clinical studies conducted for an approved product. FDA may also require companies to perform additional studies or measurements to support the change from the approved product. FDA may then approve the new product candidate for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

To the extent that a Section 505(b)(2) NDA relies on studies conducted for a previously approved drug product, the applicant is required to certify to FDA concerning any patents listed for the approved product in FDA Orange Book. FDA Orange Book is where patents associated with an FDA-approved product are listed. Specifically, the applicant must certify for each listed patent that (1) the required patent information has not been filed; (2) the listed patent has expired; (3) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (4) the listed patent is invalid, unenforceable or will not be infringed

by the new product. A certification that the new product will not infringe the already approved product's listed patent or that such patent is invalid is known as a Paragraph IV certification. If the applicant does not challenge the listed patents through a Paragraph IV certification, the Section 505(b)(2) NDA application will not be approved until all the listed patents claiming the referenced product have expired. The Section 505(b)(2) NDA application also will not be accepted or approved until any non-patent exclusivity, such as exclusivity for obtaining approval of a New Chemical Entity, listed in the Orange Book for the referenced product has expired.

If the 505(b)(2) NDA applicant has provided a Paragraph IV certification to FDA, the applicant must also send notice of the Paragraph IV certification to the referenced NDA and patent holders once the 505(b)(2) NDA has been accepted for filing by FDA. The NDA and patent holders may then initiate a legal challenge to the Paragraph IV certification. Under the FFDCA, the filing of a patent infringement lawsuit within 45 days of the NDA and patent holders' receipt of a Paragraph IV certification in most cases automatically prevents FDA from approving the Section 505(b)(2) NDA for 30 months, or until a court decision or settlement finding that the patent is invalid, unenforceable or not infringed, whichever is earlier. The court also has the ability to shorten or lengthen the 30-month stay if either party is found not to be reasonably cooperating in expediting the litigation. Thus, the Section 505(b)(2) applicant may invest a significant amount of time and expense in the development of its product only to be subject to significant delay and patent litigation before its product may be commercialized.

The 505(b)(2) NDA applicant also may be eligible for its own regulatory exclusivity period, such as three-year exclusivity. Specifically, a product may be granted three-year Hatch-Waxman exclusivity if one or more clinical studies, other than bioavailability or bioequivalence studies, was essential to the approval of the application and was conducted/sponsored by the applicant. Should this occur, FDA would be precluded from making effective any other application for the same condition of use or for a change to the drug product that was granted exclusivity until after that three-year exclusivity period has expired. Additional non-patent exclusivities may also apply.

Additionally, the 505(b)(2) NDA applicant may have relevant patents in the Orange Book, and if so, it can initiate patent infringement litigation against those applicants that challenge such patents, which could result in a 30-month stay delaying those applicants.

Manufacturing Requirements

We and our third-party manufacturers must comply with applicable FDA regulations relating to FDA's cGMP regulations including applicable QSR requirements. The cGMP regulations include requirements relating to, among other things, organization of personnel, buildings and facilities, equipment, control of components and drug product containers and closures, production and process controls, packaging and labeling controls, holding and distribution, laboratory controls, records and reports, and returned or salvaged products. The manufacturing facilities for our products must meet cGMP requirements to the satisfaction of FDA pursuant to a pre-approval inspection before we can use them to manufacture our products. We and our third-party manufacturers are also subject to periodic unannounced inspections of facilities by FDA and other authorities, including procedures and operations used in the testing and manufacture of our products to assess our compliance with applicable regulations. Failure to comply with statutory and regulatory requirements subjects a manufacturer to possible legal or regulatory action, including, among other things, warning letters, the seizure or recall of products, injunctions, consent decrees placing significant restrictions on or suspending manufacturing operations and civil and criminal penalties.

Other Regulatory Requirements

We are also subject to various laws and regulations regarding laboratory practices, the experimental use of animals, and the use and disposal of hazardous or potentially hazardous substances in connection with our research. In each of these areas, as above, FDA has broad regulatory and enforcement powers, including, among other things, the ability to levy fines and civil penalties, suspend or delay issuance of approvals, seize or recall products, and withdraw approvals, any one or more of which could have a material adverse effect on us.

Coverage and Reimbursement

Sales of our products, if approved, will depend, in part, on the extent to which our products will be covered by third-party payors, such as government health care programs, commercial insurance and managed healthcare organizations. These third-party payors are increasingly limiting coverage and reducing reimbursements for medical products and services. In addition, the U.S. government, state legislatures and foreign governments have continued implementing cost-containment programs, including price controls, restrictions on coverage and reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. Decreases in third-party reimbursement for our drug candidates or a decision by a third-party payor to not cover our drug candidates could reduce physician utilization of our products and have a material adverse effect on our sales, results of operations and financial condition.

Other Healthcare Laws

Although we currently do not have any products on the market, if our drug candidates are approved and we begin commercialization, we will be subject to healthcare regulation and enforcement by the federal government and the states and foreign governments in which we conduct our business. These laws include, without limitation, state and federal anti-kickback, fraud and abuse, false claims, privacy and security, and physician sunshine laws and regulations.

The federal Anti-Kickback Statute prohibits, among other things, any person from knowingly and willfully offering, soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual, for an item or service or the purchasing or ordering of a good or service, for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs. The Anti-Kickback Statute is subject to evolving interpretations. In the past, the government has enforced the Anti-Kickback Statute to reach large settlements with healthcare companies based on sham consulting and other financial arrangements with physicians. Further, 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 government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal 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.

Additionally, the False Claims Act prohibits knowingly presenting or causing the presentation of a false, fictitious or fraudulent claim for payment to the U.S. government. Actions under the 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 False Claims Act can result in very significant monetary penalties and treble damages. The federal government is using the False Claims Act, and the accompanying threat of significant liability, in its investigation and prosecution of pharmaceutical and biotechnology companies throughout the country, for example, in connection with the promotion of products for unapproved uses and other sales and marketing practices. The government has obtained multi-million and multi-billion dollar settlements under the False Claims Act in addition to individual criminal convictions under applicable criminal statutes. Given the significant size of actual and potential settlements, it is expected that the government will continue to devote substantial resources to investigating healthcare providers' and manufacturers' compliance with applicable fraud and abuse laws.

The federal criminal false claims laws prohibit, among other things, knowingly and willfully making, or causing to be made, a false statement or representation of a material fact for use in determining the right to any benefit or payment under a federal health care program. A violation of these laws may constitute a felony or misdemeanor and may result in fines or imprisonment.

The federal Civil Monetary Penalties Law prohibits, among other things, the offering or transferring of remuneration to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary's selection of a particular supplier of Medicare or Medicaid payable items or services. Noncompliance with such beneficiary inducement provision of the federal Civil Monetary Penalties Law can result in civil money penalties for each wrongful act, assessment of three times the amount claimed for each item or service and exclusion from the federal healthcare programs.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, also created new 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 federal Anti-Kickback Statute, 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.

We may also be subject to data privacy and security regulation by both the federal government and the states in which we conduct our 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.

In addition, there has been a recent trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or

collectively, the Affordable Care Act, among other things, imposes new reporting requirements on certain drug manufacturers for payments made by them to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in civil monetary penalties of up to an aggregate of $169,170 per year (or up to an aggregate of $1.127 million per year for "knowing failures"), for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission. Drug manufacturers are required to submit reports to the government by the 90th day of each calendar year. Certain states also mandate implementation of commercial compliance programs, impose restrictions on drug manufacturer marketing practices and/or require the tracking and reporting of marketing expenditures and pricing information, as well as gifts, compensation and other remuneration to physicians.

The shifting commercial compliance environment and the need to build and maintain robust and expandable systems to comply with different compliance and/or reporting requirements in multiple jurisdictions increase the possibility that a healthcare company may violate one or more of the requirements. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs and imprisonment, any of which could adversely affect our ability to operate our business and our financial results.

Healthcare Reform

In March 2010, the Affordable Care Act, which substantially changed the way healthcare is financed by both governmental and private insurers in the United States, was signed into law and significantly affected the pharmaceutical industry. The Affordable Care Act contains a number of provisions, including those governing enrollment in federal healthcare programs, reimbursement adjustments and fraud and abuse changes. Additionally, the Affordable Care Act increases the minimum level of Medicaid rebates payable by manufacturers of brand name drugs from 15.1% to 23.1%; imposes a non-deductible annual fee on pharmaceutical manufacturers or importers who sell "branded prescription drugs" to specified federal government programs; and addresses 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. Since its enactment, there have been judicial and Congressional challenges to certain aspects of the Affordable Care Act, and we expect there will be additional challenges and amendments to the Affordable Care Act in the future. For example, on December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, ruled that the individual mandate is a critical and inseverable feature of the Affordable Care Act, and therefore, because it was repealed as part of the Tax Cuts and Jobs Act, the remaining provisions of the Affordable Care Act are invalid as well. While the Trump Administration and the Centers for Medicare & Medicaid Services have both stated that the ruling will have no immediate effect, it is unclear how this decision, subsequent appeals, if any, will impact the law.

Other legislative changes have been proposed and adopted since the Affordable Care Act was enacted, including aggregate reductions of Medicare payments to providers of 2% per fiscal year and reduced payments to several types of Medicare providers. Moreover, there has recently been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several 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 drug products. Individual states in the United States have also become increasingly active in implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

Employees

As of February 28, 2019, we had six full-time employees and several consultants in the regulatory, clinical, manufacturing and finance areas. None of our employees are represented by a collective bargaining arrangement, and we believe our relationship with our employees is good.

About Evoke

We were formed as a Delaware corporation in January 2007. Our principal executive offices are located at 420 Stevens Avenue, Suite 370, Solana Beach, California 92075, and our telephone number is (858) 345-1494.

Financial Information about Segments

We have one operating segment, which is the development of pharmaceutical products. See Note 2 to our financial statements included in this Annual Report on Form 10-K. For financial information regarding our business, see "Management's Discussion and Analysis of Financial Condition and Results of Operations" and those financial statements and related notes.

Available Information

We file electronically with the Securities and Exchange Commission, or SEC, our annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended. We make available copies of these reports, free of charge, on our website at www.evokepharma.com, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. The SEC maintains a website that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. The address of that website is www.sec.gov. The information in or accessible through the SEC and our website are not incorporated into, and are not considered part of, this report. Further, our references to the URLs for these websites are intended to be inactive textual references only.

Item 1A. Risk Factors

We operate in a dynamic and rapidly changing environment that involves numerous risks and uncertainties. Certain factors may have a material adverse effect on our business prospects, financial condition and results of operations, and you should carefully consider them. Accordingly, in evaluating our business, we encourage you to consider the following discussion of risk factors, in its entirety, in addition to other information contained in this Annual Report on Form 10-K and our other public filings with the Securities and Exchange Commission, or SEC. Other events that we do not currently anticipate or that we currently deem immaterial may also affect our business, prospects, financial condition and results of operations.

Risks Related to our Business, including the Development, Regulatory Approval and Potential Commercialization of our Product Candidate, Gimoti

Our business is entirely dependent on the success of Gimoti, which failed to achieve the primary endpoint of symptom improvement in a Phase 3 clinical trial in female patients with symptoms associated with diabetic gastroparesis. While we are continuing to pursue regulatory approval based on the results of our completed comparative exposure PK trial, we cannot be certain that we will be able to obtain regulatory approval for, or successfully commercialize, Gimoti.

To date, we have devoted all of our research, development and clinical efforts and financial resources toward the development of Gimoti, our patented nasal delivery formulation of metoclopramide for the relief of symptoms associated with acute and recurrent diabetic gastroparesis in adult women. Gimoti is our only product candidate. In July 2016, we announced topline results from our Phase 3 clinical trial that evaluated the efficacy and safety of Gimoti in women with symptoms associated with diabetic gastroparesis. In this study, Gimoti did not achieve its primary endpoint of symptom improvement in the Intent-to-Treat (ITT) group at Week 4.

In December 2016, we announced the completion of a pre-NDA meeting with FDA, in which FDA agreed that a comparative exposure PK trial was acceptable as a basis for submission of a Gimoti NDA. Data from the comparative exposure PK trial will serve as a portion of the 505(b)(2) data package to include prior efficacy and safety data developed by us and FDA's prior findings of safety and efficacy for the Listed Drug, Reglan Tablets 10 mg. In October 2017, we announced positive topline results from the comparative exposure PK trial. In addition, based on feedback received from FDA at an additional pre-NDA meeting, we proposed a risk mitigation strategy and post-approval safety trial as part of the NDA we submitted for Gimoti to FDA on June 1, 2018. We received a Day-74 filing communication letter in August 2018 that stated that the NDA was sufficiently complete to permit a substantive review and set a target goal date under PDUFA of April 1, 2019. On March 1, 2019, we received a DRL from FDA, which provided preliminary notice of certain deficiencies identified during FDA's initial review of the Gimoti NDA. Specifically, the DRL described concerns with the information provided in the NDA, including concerns that insufficient evidence had been offered regarding product quality control and reproducibility specific to the commercially available sprayer device used with Gimoti, that there is a lack of adequate information to support sex-based efficacy claims and that the pharmacology data provided may not demonstrate bioavailability to the Listed Drug, Reglan Tablets 10 mg. Although a DRL reflects preliminary comments that are subject to change and does not reflect FDA's final decision on the NDA, approval of Gimoti by the PDUFA date of April 1, 2019, if any, is uncertain given the letter. We plan to respond to the deficiencies raised in the DRL to allow time for FDA to potentially complete its review prior to the PDUFA date, however, there is no guarantee that we will be able to adequately address these deficiencies to FDA's satisfaction or that FDA will be able to consider our response before it takes final action on the NDA. The receipt of the DRL increases the risk that we may receive a CRL based on the deficiencies raised in the DRL or other issues identified by FDA as it completes its review of the NDA.

Because our business is entirely dependent on the success of Gimoti, if we are unable to successfully complete development of and receive regulatory approval of this product candidate, we will be required to curtail all of our activities and may be required to liquidate, dissolve or otherwise wind down our operations. Any of these events could result in the complete loss of an investment in our securities.

In addition to the above factors, the future regulatory and commercial success of Gimoti is subject to a number of additional risks, including the following:

- we may not be able to provide acceptable evidence of safety and efficacy for Gimoti, including as a result of the proposed duration of use for Gimoti being shorter as compared to the maximum approved dosing duration for the referenced Listed Drug, Reglan Tablets 10 mg.;
- the results of our clinical trials may not meet the level of statistical or clinical significance or other bioequivalence parameters required by FDA for marketing approval, including C_{max} falling below the equivalence range in the comparative exposure PK trial;
- FDA may not agree with the analysis of our clinical trial results, including our analysis of results of the PK trial;
- we may be required to undertake additional clinical trials and other studies of Gimoti before we receive approval of the NDA we submitted;

- we may not have sufficient financial and other resources to complete clinical development for Gimoti;
- if approved, Gimoti will compete with well-established products already approved for marketing by FDA, including oral and intravenous forms of metoclopramide, the same active ingredient in the nasal spray for Gimoti;
- our reliance on NGP and any third-party sales organization to commercialize Gimoti, if approved;
- we may not be able to maintain commercial manufacturing arrangements with third-party manufacturers or establish and maintain commercial-scale manufacturing capabilities;
- FDA may disagree with the design of any future clinical trials, if any are necessary;
- variability in subjects, adjustments to clinical trial procedures and inclusion of additional clinical trial sites;
    - subjects in our clinical trials may die or suffer other adverse effects for reasons that may or may not be related to Gimoti, such as dysgeusia, headache, diarrhea, nasal discomfort, tremor, myoclonus, somnolence, rhinorrhea, throat irritation, and fatigue; and
- we may not be able to obtain, maintain and enforce our patents and other intellectual property rights.

Of the large number of drugs in development in this industry, only a small percentage result in the submission of an NDA to FDA and even fewer are approved for commercialization. Furthermore, even if we do receive regulatory approval to market Gimoti, any such approval may be subject to limitations on the indicated uses for which we may market the product.

We may require substantial additional funding and may be unable to raise capital when needed, which would force us to liquidate, dissolve or otherwise wind down our operations.

Our operations have consumed substantial amounts of cash since inception. We believe, based on our current operating plan, that our existing cash and cash equivalents, along with proceeds from the NGP Working Capital Loan and the NGP Credit Agreement which will be available only if Gimoti is approved by FDA, may extend our cash runway into 2020, without accounting for any future Gimoti product revenue, although there can be no assurance in that regard. If we are unable to receive approval of the Gimoti NDA, and if we are unable to secure capital under the NGP Working Capital Loan or the NGP Credit Agreement, we believe that our existing cash and cash equivalents will be sufficient to fund our operations until July 2019. Under either situation, we may be required to raise additional funds in order to continue as a going concern. There can be no assurance that we will be able to further develop Gimoti, if required. Because our business is entirely dependent on the success of Gimoti, if we are unable to secure additional financing or identify and execute on other development or strategic alternatives for Gimoti or our company, we will be required to curtail all of our activities and may be required to liquidate, dissolve or otherwise wind down our operations. Any of these events could result in a complete loss of your investment in our securities.

Our estimates of the amount of cash necessary to fund our activities may prove to be wrong and we could spend our available financial resources much faster than we currently expect. Our future funding requirements will depend on many factors, including, but not limited to:

- the need for, and the progress, costs and results of, any additional clinical trials of Gimoti that may be required by FDA, including any pre-approval or post-approval trials FDA or other regulatory agencies may require evaluating the efficacy or safety of Gimoti;
- the costs involved for additional data collection and analysis to respond to FDA questions related to the NDA and to respond to the DRL;
- the outcome, costs and timing of seeking and obtaining regulatory approvals from FDA, and any similar regulatory agencies;
- the costs and timing of completion of outsourced commercial manufacturing supply arrangements for Gimoti;
- the costs required to commercialize Gimoti, including expenses incurred under our commercialization agreement with NGP, and the costs of establishing or outsourcing additional sales, marketing and distribution capabilities;
- the commercial success of Gimoti, if approved;
- the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights associated with Gimoti;
- the terms and timing of any collaborative, licensing, co-promotion or other arrangements that we may establish; and

- costs associated with any other product candidates that we may develop, in-license or acquire.

Additional funding may not be available to us on acceptable terms or at all. In addition, the terms of any financing may adversely affect the holdings or the rights of our stockholders. Furthermore, the issuance of additional shares or other securities by us, or the possibility of such issuance, may cause the market price of our shares to decline and dilute the holdings of our existing stockholders. If we raise additional funds by incurring debt, the terms of the debt may involve significant cash payment obligations, as well as covenants and specific financial ratios that may restrict our ability to operate our business. We cannot provide any assurance that our existing capital resources will be sufficient to enable us to identify or execute a viable plan for continued clinical development of Gimoti or to otherwise survive as a going concern.

Topline data may not accurately reflect the complete results of a particular study or trial.

We may publicly disclose topline or interim data from time to time, which is based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the topline results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Topline data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, topline data should be viewed with caution until the final data are available.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our company in general. For example, while we believe that the AUC measurement was the most clinically relevant PK parameter for our comparative exposure PK trial, FDA may disagree or may emphasize other data such as C_{max} falling below the equivalence range of the Listed Drug, Reglan Tablets 10 mg. Any contrary views by FDA would impact our dose selection and FDA's review of the NDA. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular drug, drug candidate or our business. If the topline data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, operating results, prospects or financial condition. Further, although we reported positive topline data for the PK trial, FDA may still require the conduct of additional efficacy or safety trials.

If we are not able to obtain regulatory approval for Gimoti, we will not be able to commercialize this product candidate and our ability to generate revenue will be limited.

We have submitted an NDA for Gimoti, but have not received regulatory approval to market any product candidates in any jurisdiction. We are not permitted to market Gimoti in the United States until we receive approval of an NDA for Gimoti in a particular indication from FDA. To date, we have completed a Phase 1 bioavailability and pharmacokinetics trial, a comparative exposure PK trial, a Phase 3 clinical trial in female subjects, a companion Phase 3 clinical trial in male subjects, a Thorough ECG (QT/QTc) study, a Phase 2b clinical trial and we acquired the results from a separate Phase 2 clinical trial in diabetic subjects with gastroparesis. In the Phase 2b clinical trial that we performed ourselves, which concluded in 2011, Gimoti failed to meet the primary endpoint for the trial. Although an overall improvement in symptoms was observed in Gimoti-treated subjects with diabetic gastroparesis compared to placebo in this Phase 2b clinical trial, the difference was not statistically significant due to a high placebo response among male subjects. The earlier Phase 2 clinical trial performed by Questcor was a multicenter, randomized, open-label, parallel design study. This head-to-head study compared the efficacy and safety of two doses of

metoclopramide nasal spray, 10 mg and 20 mg, with FDA-approved 10 mg metoclopramide tablet. Although data from the earlier Phase 2 clinical trial was referenced in the Gimoti NDA, the open-label study design limits the importance of the efficacy results in the NDA.

We completed our Phase 3 clinical trial in female subjects with symptoms associated with acute and recurrent diabetic gastroparesis and announced in July 2016 that Gimoti did not achieve its primary endpoint of symptom improvement at Week 4. While we submitted the results from the comparative exposure PK trial as a portion of the 505(b)(2) NDA submission that included prior efficacy and safety data developed by us along with FDA's prior findings of safety and efficacy for the Listed Drug, Reglan Tablets 10 mg., there is no guarantee that regulators will agree with our assessment of the clinical trials for Gimoti conducted to date, including the comparative exposure PK trial. In addition, we have only limited experience in filing the applications necessary to gain regulatory approvals and expect to rely on consultants and third-party contract research organizations to assist us in this process. FDA and other regulators have substantial discretion in the approval process and may decide that our data are insufficient for approval and require additional clinical trials, or preclinical or other studies.

Varying interpretation of the data obtained from preclinical and clinical testing could delay, limit or prevent regulatory approval of a product candidate. Furthermore, we have acquired our rights to Gimoti from Questcor, who acquired its rights from a previous sponsor of the IND. Thus, the preclinical and a portion of the clinical data relating to Gimoti that we submitted in the NDA for Gimoti was obtained from studies conducted before we owned the rights to the product candidate and, accordingly, that were prepared and managed by predecessors. These predecessors may not have applied the same resources and given the same attention to this development program as we would have if we had been in control from inception.

Gimoti and the activities associated with its development and potential commercialization, including its testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by FDA and other regulatory agencies in the United States and by comparable authorities in other countries. Failure to obtain regulatory marketing approval for Gimoti will prevent us from commercializing the product candidate, and our ability to generate revenue will be materially impaired.

FDA may impose requirements on our clinical trials that are difficult to comply with, which could harm our business.

In July 2015, FDA published draft guidance intended to assist sponsors in the clinical development of drugs for the treatment of diabetic and idiopathic gastroparesis clinical trials, Gastroparesis: Clinical Evaluation of Drugs for Treatment – Guidance for Industry. We believe that FDA Guidance is consistent with the advice FDA provided to us regarding trial design and study endpoints for our completed Phase 3 trials. In addition, FDA Guidance explicitly states that there is an urgent medical need for development of drugs with a favorable risk-benefit profile to treat patients with gastroparesis and acknowledges that "patients with diabetic gastroparesis may experience further derangement of glucose control because of unpredictable gastric emptying and altered absorption of orally administered hypoglycemic drugs." FDA Guidance, however, does not create or confer any rights for or on any person and do not operate to bind FDA or the public, and FDA may ultimately disagree with our interpretation regarding the meaning or applicability of any published Guidance documents.

We conducted a Phase 3 trial in adult female subjects with diabetic gastroparesis, which failed to reach its primary endpoint. However, following our second pre-NDA meeting with FDA in December 2016, FDA agreed that a comparative exposure PK trial, along with prior efficacy and safety data from other completed Gimoti studies, would be appropriate for NDA submission seeking an indication of treatment of symptoms associated with diabetic gastroparesis in women. Although the results from the comparative exposure PK trial along with the prior data were sufficient to submit an NDA for Gimoti in June 2018, it is possible FDA will require additional clinical testing before approval of the NDA. In addition, based on discussions with FDA, we also conducted a similar study for safety and efficacy in adult male subjects with diabetic gastroparesis. A portion of the safety and efficacy data from this trial was submitted as a part of the NDA. If we are unable to comply with FDA's requirements, we will not be able to obtain approval for Gimoti and our ability to generate revenue will be materially impaired.

Any termination or suspension of, or delays in the completion of, any future clinical trials could result in increased costs to us, delay or limit our ability to generate revenue and adversely affect our commercial prospects.

Delays in the completion of any future clinical trials for Gimoti could significantly affect our product development costs. We do not know whether any trials will produce data on schedule, if at all. The commencement and completion of clinical trials can be delayed for a number of reasons, including delays related to:

- FDA placing a clinical trial on hold;
- subjects failing to remain in our trial at the rate we expect (for example, due to variable patient frequency and severity of disease and variability in gastric emptying testing);
- subjects choosing an alternative treatment for the indication for which we are developing Gimoti, or participating in competing clinical trials;
- subjects experiencing severe or unexpected drug-related adverse effects;

- a facility manufacturing Gimoti, or any of its components, being ordered by FDA or other government or regulatory authorities to temporarily or permanently shut down due to violations of FDA's cGMP or other applicable requirements, or infections or cross-contaminations of a product candidate in the manufacturing process;
- any changes to our manufacturing process that may be necessary or desired;
- third-party clinical investigators losing their license or permits necessary to perform our clinical trials, not performing our clinical trials on our anticipated schedule or consistent with the clinical trial protocol, good clinical practice and regulatory requirements, or other third parties not performing data collection and analysis in a timely or accurate manner;
- inspections of clinical trial sites by FDA or the finding of regulatory violations by FDA or an independent institutional review board, or IRB, that require us to undertake corrective action, result in suspension or termination of one or more sites

or the imposition of a clinical hold on the entire trial, or that prohibit us from using some or all of the data in support of our marketing applications;

- third-party contractors becoming debarred or suspended or otherwise penalized by FDA or other government or regulatory authorities for violations of regulatory requirements, in which case we may need to find a substitute contractor, and we may not be able to use some or any of the data produced by such contractors in support of our marketing applications; or
- one or more IRBs refusing to approve, suspending or terminating the trial at an investigational site, precluding enrollment of additional subjects, or withdrawing its approval of the trial.

Product development costs will increase if we have delays in testing or approval of Gimoti, or if we need to perform more or larger clinical trials than planned. Additionally, changes in regulatory requirements and policies may occur and we may need to amend clinical trial protocols to reflect these changes. Amendments may require us to resubmit our clinical trial protocols to IRBs for reexamination, which may impact the costs, timing or successful completion of a clinical trial. If we experience delays in completion of or if we, FDA or other regulatory authorities, the IRB, or other reviewing entities, or any of our clinical trial sites suspend or terminate any of our clinical trials, the commercial prospects for our product candidate may be harmed and our ability to generate product revenues will be delayed. In addition, many of the factors that cause, or lead to, termination or suspension of, or a delay in the commencement or completion of, clinical trials may also ultimately lead to the denial of regulatory approval of a product candidate. Also, if one or more clinical trials are delayed, our competitors may be able to bring products to market before we do, and the commercial viability of Gimoti could be significantly reduced.

Delays in the completion of any clinical trials and studies we may conduct for Gimoti could be harmful to our business and cause us to require additional funding.

Final marketing approval for Gimoti by FDA or other regulatory authorities for commercial use may be delayed, limited, or denied, any of which would adversely affect our ability to generate operating revenues.

We submitted an NDA for Gimoti in June 2018. Under PDUFA, FDA is subject to a two-tiered system of review times – Standard Review and Priority Review. For drugs subject to standard review, such as Gimoti, FDA has a goal to complete its review of the NDA and respond to the applicant within ten months from the date of receipt of an NDA. In its Day-74 filing communication letter, FDA assigned a target goal date under PDUFA of April 1, 2019 for the Gimoti NDA. The review process and the PDUFA goal date may be extended if FDA requests or the NDA sponsor otherwise provides additional information or clarification regarding information already provided in the submission prior to the PDUFA target goal date. FDA's review goals are subject to change, and it is unknown whether the review of the NDA will be completed within FDA's review goals or will be delayed. For example, on March 1, 2019, we received a DRL from FDA, which provided preliminary notice of certain deficiencies identified during FDA's initial review of the Gimoti NDA. We plan to respond to the deficiencies raised in the DRL to allow time for FDA to potentially complete its review prior to the PDUFA date. There is no guarantee, however, that we will be able to address these deficiencies to FDA's satisfaction or that FDA will be able to consider our response before it takes final action on the NDA. The receipt of the DRL increases the risk that we may receive a CRL based on the deficiencies raised in the DRL or other issues identified by FDA as it completes its review of the NDA. Even if we are able to address FDA's concerns in a timely manner, the length of time needed for FDA to complete its review of the NDA may be significantly extended.

Moreover, the duration of FDA's review may depend on the number and type of other NDAs that are submitted with FDA around the same time period. In addition, FDA may refer applications for novel drug products or drug products which present difficult questions of safety or efficacy to an advisory committee for review, evaluation and recommendation as to whether the application should be approved and under what conditions. FDA is not bound by the recommendation of an advisory committee, but it considers such recommendations carefully when making decisions.

We cannot provide any assurance as to whether or when we will obtain regulatory approval to commercialize Gimoti. We cannot, therefore, predict the timing of any future revenue. Because Gimoti is our only product candidate this risk

is particularly significant for us. We cannot commercialize Gimoti until the appropriate regulatory authorities have reviewed and approved marketing applications for this product candidate. We cannot assure you that the regulatory agencies will complete their review processes in a timely manner or that we will obtain regulatory approval for Gimoti. In addition, we may experience delays or the application may be rejected based upon additional government regulation from future legislation or administrative action or changes in FDA policy during the period of product development, clinical trials and FDA regulatory review. For example, in 2009 following an FDA review of metoclopramide spontaneous safety reports, FDA required a boxed warning be added to the metoclopramide product label concerning the chance of tardive dyskinesia, or TD, for patients taking these products. FDA requires a boxed warning (sometimes referred to as a “Black Box” Warning) for products that have shown a significant risk of severe or life-threatening adverse events. Recently, the European Medicines Agency’s Committee on Medicinal Products for Human Use, or CHMP, has reviewed and has proposed labeling changes for marketed metoclopramide products in the European Union based on age, dosing guidelines or indications. Based on their assessment of the limited efficacy and safety data currently available to the CHMP, the CHMP recommended to the European Medicines Agency that indications with limited or inconclusive efficacy data, including GERD, dyspepsia and gastroparesis, be removed from the approved product label in the European Union. There can be no assurance as to whether FDA will re-review

approved metoclopramide product labels as a result of any such regulatory actions in the European Union or otherwise. If marketing approval for Gimoti is delayed, limited or denied, our ability to market the product candidate, and our ability to generate product sales, would be adversely affected.

In addition, in a written communication, FDA responded to our request for proprietary name review by conditionally accepting our proposed proprietary brand name, Gimoti. However, FDA could still fail to finally approve this proprietary name through the NDA review process. FDA typically conducts a rigorous review of proposed product names, including an evaluation of potential for confusion with the names of other products, which could lead to identification of the wrong medication or other prescribing, ordering, dispensing, administration, or monitoring errors. FDA may also object to a product name if it believes the name functions to overstate the efficacy, minimize the risk, broaden the proposed indication, make unsubstantiated superiority claims, or is otherwise false or misleading. If FDA objects to the product name Gimoti as part of the NDA review process, we may be required to adopt an alternative name for our product candidate. If we adopt an alternative name, we would lose the benefit of our existing trademark applications for Gimoti and may be required to expend significant additional resources in an effort to identify a suitable product name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to FDA. We may be unable to build a successful brand identity for a new trademark in a timely manner or at all, which would limit our ability to commercialize our product candidate.

We have no internal sales, marketing or distribution capabilities currently and will rely on NGP and other third parties for the commercialization of Gimoti, and we and they may not be able to effectively market, sell and distribute Gimoti, if approved.

Currently, we have no internal sales, marketing or distribution capabilities. If Gimoti ultimately receives regulatory approval, we may not be able to effectively market and distribute the product candidate. We have engaged NGP to manage the commercial operations for a dedicated sales team to market Gimoti. We anticipate engaging a third-party sales organization to retain, train and deploy this direct sales force. We may not be able to hire consultants or external service providers to assist us in retaining, training and deploying a sales force or for other sales, marketing and distribution functions on acceptable financial terms or at all. If we fail to engage with a third party on acceptable terms or at all, we will have to invest significant amounts of financial and management resource to develop internal sales, distribution and marketing capabilities. We have no experience in retaining, training or deploying a sales force and no experience in managing third-party sales organizations. Further, we or the third-party sales organization may be unable to identify and retain suitable candidates to fill our direct sales force needs, on our expected launch timeframe or otherwise. To the extent we or the third-party sales organization are not successful in retaining qualified sales and marketing personnel, we may not be able to effectively market Gimoti. Further, there can be no assurance that the capabilities of the NGP and the third-party sales organizations will effective in marketing and selling Gimoti, or that their personnel will be more effective than an internally developed sales organization. In addition, NGP can terminate our agreement under certain circumstances, including failure to make payments when due, if we are in material breach of the agreement and fail to remedy the breach following notice, if we enter into bankruptcy, or if we are excluded from participation in certain federal governmental programs or have similar actions taken against us. If we, or either NGP or the third-party sales organization, fails to hire, train, retain and manage qualified sales personnel, market our product successfully or on a cost-effective basis or otherwise terminates our relationship, our ability to generate revenue will be limited and we will need to identify and retain an alternative organization, or develop our own sales and marketing capability. In such an event, we would have to invest significant amounts of financial and management resources to develop internal sales, distribution and marketing capabilities. This could involve significant delays and costs, including the diversion of our management’s attention from other activities. We may also need to retain additional consultants or external service providers to assist us in sales, marketing and distribution functions, and may be unsuccessful in retaining such services on acceptable financial terms or at all.

If we do perform sales, marketing and distribution functions ourselves, we could face a number of additional related risks, including:

- inability to attract and build an effective marketing department or sales force;
- the cost of establishing a marketing department or sales force may exceed our available financial resources and the revenues generated by Gimoti or any other product candidates that we may develop, in-license or acquire; and
- our direct sales and marketing efforts may not be successful.

If we are unsuccessful in building and managing a sales and marketing infrastructure internally or through a third-party partner for any approved product, we will have difficulty commercializing the product, which would adversely affect our business and financial condition.

Changes in funding for FDA and other government agencies could hinder their ability to hire and retain key leadership and other personnel, or otherwise prevent new products and services from being developed or commercialized in a timely manner, which could negatively impact our business.

The ability of FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of other government agencies that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including for 35 days beginning on December 22, 2018, the U.S. government has shut down several times and certain regulatory agencies, such as FDA, have had to furlough critical FDA employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

If the requirements under Section 505(b)(2) are not as we expect, the approval pathway for our primary product candidate will likely take significantly longer, cost significantly more and entail significantly greater complications and risks than anticipated, and in either case may not be successful.

We are seeking FDA approval through the Section 505(b)(2) regulatory pathway for our primary product candidate, Gimoti. Gimoti is a drug/device combination product that will be regulated under the drug provisions of the FFDCA, which enabled us to submit an NDA seeking its approval. The Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Amendments, added Section 505(b)(2) to the FFDCA. Section 505(b)(2) permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference.

If the requirements under Section 505(b)(2) are not as we expect, we may need to conduct additional clinical trials, provide additional data and information and meet additional standards for regulatory approval. If this were to occur, the time and financial resources required to obtain FDA approval for Gimoti, and the complications and risks associated with our lead product candidate, would likely substantially increase. We may need to obtain additional funding, which could result in significant dilution to the ownership interests of our then existing stockholders to the extent we issue equity securities or convertible debt. We cannot assure you that we would be able to obtain such additional financing on terms acceptable to us, if at all. Moreover, inability to meet the requirements of Section 505(b)(2) could result in competitive products reaching the market before Gimoti, which could impact our competitive position and prospects. Even if we meet the requirements of Section 505(b)(2), we cannot be assured that Gimoti or any future product candidates will receive the requisite approvals for commercialization.

Even if we obtain marketing approval for Gimoti, it could be subject to restrictions or withdrawal from the market and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our product candidate, when and if Gimoti is approved.

Even if U.S. regulatory approval is obtained, FDA may still impose significant restrictions on Gimoti's indicated uses or marketing or impose ongoing requirements for potentially costly and time-consuming post-approval studies, post-market surveillance or clinical trials. For example, FDA requested we include a proposal for a post-marketing safety trial as part of the NDA submission. Gimoti will also be subject to ongoing FDA requirements governing the labeling, packaging, storage, distribution, safety surveillance, advertising, promotion, recordkeeping and reporting of safety and other post-market information. In addition, manufacturers of drug products and their facilities are subject to continual review and periodic inspections by FDA and other regulatory authorities for compliance with cGMP requirements relating to quality control, quality assurance and corresponding maintenance of records and documents. If we or a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions on that product, the manufacturing facility or us, including requesting recall or withdrawal of the product from the market or suspension of manufacturing.

If we or the manufacturing facilities for Gimoti fail to comply with applicable regulatory requirements, a regulatory agency may:

- issue warning letters or untitled letters;
- seek an injunction or impose civil or criminal penalties or monetary fines;

- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve pending applications or supplements or applications filed by us;
- suspend or impose restrictions on operations, including costly new manufacturing requirements; or
- seize or detain products, refuse to permit the import or export of product, or request us to initiate a product recall.

The occurrence of any event or penalty described above may inhibit our ability to commercialize our products and generate revenue.

FDA has the authority to require a REMS as a condition of approval of an NDA or following approval, which may impose further requirements or restrictions on the distribution or use of an approved drug, such as limiting prescribing to certain physicians or

medical centers that have undergone specialized training, limiting treatment to patients who meet certain safe-use criteria and requiring treated patients to enroll in a registry. In March 2009, FDA informed drug manufacturers that it will require a REMS for metoclopramide drug products, including a Medication Guide, elements to assure safe use (including an education program for prescribers and materials for prescribers to educate patients), and a timetable for submission of assessments of at least six months, 12 months, and annually after the REMS is approved. In addition, FDA requested we include a proposal for a risk mitigation strategy in the NDA submission. We proposed elements of a REMS and a post-approval safety trial within the NDA for Gimoti. At this time, the elements of the REMS that FDA will require for Gimoti are uncertain as there are varying levels of requirements that may include a Medication Guide, similar to the Listed Drug, Reglan Tablets 10 mg., and other elements, such as a communication plan and an implementation plan, designed to ensure safe use, as well as a timetable for submission of post-marketing assessments after the REMS is approved.

In addition, if Gimoti is approved, the product labeling, advertising and promotion would be subject to regulatory requirements and continuing regulatory review. FDA strictly regulates the promotional claims that may be made about prescription products. In particular, a product may not be promoted for uses that are not approved by FDA as reflected in the product's approved labeling. If we receive marketing approval for Gimoti, physicians may nevertheless prescribe it to their patients in a manner that is inconsistent with the approved label. If we are found to have promoted such off-label uses, we may become subject to significant liability. FDA and other agencies actively enforce the laws and regulations 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 sanctions. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off-label promotion. FDA has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

FDA's policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. For example, in December 2016, the 21st Century Cures Act, or Cures Act, was signed into law. The Cures Act, among other things, is intended to modernize the regulation of drugs and spur innovation. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained, which would adversely affect our business, prospects and ability to achieve or sustain profitability.

We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. For example, certain policies of the current administration may impact our business and industry. Namely, several recent executive actions, including the issuance of a number of Executive Orders, could impose significant burdens on, or otherwise materially delay, FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. It is difficult to predict how these executive actions, including the Executive Orders, will be implemented, and the extent to which they will impact FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

Even if we receive regulatory approval for Gimoti, we still may not be able to successfully commercialize it and the revenue that we generate from its sales, if any, will be limited.

Gimoti's commercial success will depend upon the acceptance of the product candidate by the medical community, including physicians, patients and health care payors. The degree of market acceptance of our product candidate will depend on a number of factors, including:

- demonstration of clinical efficacy and safety compared to other more-established products;
- the limitation of our targeted patient population to women-only;

- limitations or warnings contained in any FDA-approved labeling, including the potential boxed warning on all metoclopramide product labels concerning the chance of TD for patients taking these products, or any limitations with respect to metoclopramide product labels in the European Union;
- acceptance of a new formulation by health care providers and their patients;
- the prevalence and severity of any adverse effects;
- new procedures or methods of treatment that may be more effective in treating or may reduce the incidences of diabetic gastroparesis;
- pricing and cost-effectiveness;
- the effectiveness of our, NGP's, or any future collaborators' sales and marketing strategies and execution;

- our ability to obtain and maintain sufficient third-party coverage and reimbursement from government health care programs, including Medicare and Medicaid, private health insurers and other third-party payors; and
- the willingness of patients to pay out-of-pocket in the absence of third-party coverage.

If Gimoti is approved, but does not achieve an adequate level of acceptance by physicians, health care payors and patients, we may not generate sufficient revenue, and we may not be able to achieve or sustain profitability. Our efforts to educate the medical community and third-party payors on the benefits of Gimoti may require significant resources and may never be successful. In addition, our ability to successfully commercialize our product candidate will depend on our ability to manufacture our products, differentiate our products from competing products and defend the intellectual property of our products.

It will be difficult for us to profitably sell Gimoti if coverage and reimbursement are limited.

Market acceptance and sales of our product candidate will depend on coverage and reimbursement policies and may be affected by healthcare reform measures. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities, pharmacy benefit managers and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors have been challenging the prices charged for products. They may also refuse to provide any coverage of uses of approved products for medical indications other than those for which FDA has granted marketing approval. This trend may impact the reimbursement for treatments for GI disorders especially, including Gimoti, as physicians typically focus on symptoms rather than underlying conditions when treating patients with these disorders and drugs are often prescribed for uses outside of their approved indications. In instances where alternative products are available, it may be required that those alternative treatment options are tried before coverage and reimbursement are available for Gimoti. Although Gimoti is a novel nasal spray formulation of metoclopramide, this is the same active ingredient that is already available in other formulations approved for the treatment of gastroparesis that are already widely available at generic prices. We cannot be sure that coverage will be available for Gimoti and, if coverage is available, the level of reimbursement. Reimbursement may impact the demand for, or the price of, this product candidate. In addition, in certain foreign countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize our product candidate.

We rely and will continue to rely on outsourcing arrangements for many of our activities, including pre-commercialization activities, regulatory submissions and supply of Gimoti.

As of February 28, 2019, we had only six full-time employees and, as a result, we rely on outsourcing arrangements with third-party vendors for a significant portion of our activities, including pre-commercial sales and marketing, data analysis, assistance with ongoing regulatory discussions and submissions supporting the Gimoti NDA, manufacturing, and the functions required of being a public company. Any failure of our third-party vendors to continue their support could adversely affect our ability to respond to issues raised by FDA’s review of the NDA and our ability to commercialize Gimoti, if approved.

The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. We do not own or operate manufacturing facilities for the production of any component of Gimoti, including metoclopramide, the nasal spray device or associated bottle, nor do we have plans to develop our own manufacturing operations in the foreseeable future. We currently depend on third-party contract manufacturers for all of our required raw materials, drug substance and drug product for our clinical trials and pre-commercialization activities, and will continue to rely on such third parties for commercial production if Gimoti is approved for marketing. We are currently using, and relying on, single suppliers and single manufacturers for starting materials, the final drug substance and nasal spray delivery device for Gimoti, including Cosma as the sole-source supplier of metoclopramide and Thermo Fisher Scientific Inc., as the sole

manufacturer of Gimoti. Although potential alternative suppliers and manufacturers for some components have been identified, we have not qualified these vendors to date. If we were required to change vendors, it could result in a failure to meet regulatory requirements or projected timelines and necessary quality standards for successful manufacturing of the various required lots of material for our development and commercialization efforts.

If we change to other manufacturers in the future, FDA and comparable foreign regulators must approve these manufacturers' facilities and processes prior to use, which could require new clinical studies, testing and compliance inspections, and the new manufactures would have to be educated in, or demonstrate successful technology transfer of, the processes necessary for the production of Gimoti.

In addition, our reliance on third-party vendors and contract manufacturing organizations, or CMOs, entails further risks including:

- non-compliance by third parties with regulatory and quality control standards;
- breach by third parties of our agreements with them;
- termination or non-renewal of an agreement with third parties; and
- sanctions imposed by regulatory authorities if compounds supplied or manufactured by a third-party supplier or manufacturer fail to comply with applicable regulatory standards.

We face substantial competition, which may result in others selling their products more effectively than we do, and in others discovering, developing or commercializing product candidates before, or more successfully, than we do.

Our future success depends on our ability to demonstrate and maintain a competitive advantage with respect to the design, development and commercialization of Gimoti. We anticipate that Gimoti, if approved, would compete directly with metoclopramide, erythromycin and domperidone, each of which is available under various trade names sold by several major pharmaceutical companies, including generic manufacturers. Metoclopramide is the only molecule currently approved in the United States to treat gastroparesis. Metoclopramide is generically-available and indicated for the relief of symptoms associated with acute and recurrent diabetic gastroparesis, without the limitation of use in women only.

Many of our potential competitors have substantially greater financial, technical and personnel resources than we have. In addition, many of these competitors have significantly greater commercial infrastructures than we have. We will not be able to compete successfully unless we successfully:

- assure health care providers, patients and health care payors that Gimoti is beneficial compared to other products in the market;
- obtain patent and/or other proprietary protection for Gimoti;
- obtain and maintain required regulatory approvals for Gimoti; and
- collaborate with others to effectively market, sell and distribute Gimoti.

Established competitors may invest heavily to quickly discover and develop novel compounds that could make our product candidate obsolete. In addition to our Gimoti product candidate, we are aware of other development candidates in clinical development. Any of these product candidates could advance through clinical development faster than Gimoti and, if approved, could attain faster and greater market acceptance than our product candidate. If we are not able to compete effectively against our current and future competitors, our business will not grow and our financial condition and operations will suffer.

If we fail to attract and retain senior management and key commercial personnel, we may be unable to successfully complete the development of Gimoti and commercialize this product candidate.

Our success depends in part on our continued ability to attract, retain and motivate highly qualified management, clinical and commercial personnel. We are highly dependent upon our senior management team composed of three individuals: David A. Gonyer, R.Ph., our President and Chief Executive Officer, Matthew J. D'Onofrio, our Executive Vice President and Chief Business Officer, and Marilyn Carlson, D.M.D., M.D., our Chief Medical Officer. The loss of services of any of these individuals could delay or prevent the successful development of Gimoti or the commercialization of this product candidate, if approved.

We may need to hire and retain qualified personnel to pursue the potential commercialization of Gimoti. We could experience problems in the future attracting and retaining qualified employees. For example, competition for qualified personnel in the biotechnology and pharmaceuticals field is intense, particularly in the San Diego, California area where we are headquartered. We may not be able to attract and retain quality personnel on acceptable terms who have the expertise we need to sustain and grow our business.

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We may encounter difficulties in managing our growth and expanding our operations successfully.

Because we only had six full-time employees as of February 28, 2019, we may need to grow our organization to pursue the potential commercialization of Gimoti and to potentially conduct additional unplanned development activities. As we seek to commercialize Gimoti, we will need to expand our regulatory, finance, manufacturing, marketing and sales capabilities or contract with third parties to provide these capabilities for us. As our operations expand, we expect that we will need to manage additional relationships with various strategic partners, suppliers and other third parties. Future growth will impose significant added responsibilities on members of management and require us to retain additional internal capabilities. Our future financial performance and our ability to commercialize Gimoti and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we must be able to manage our development efforts and clinical trials effectively and hire, train and integrate additional management, clinical and regulatory, financial, administrative and sales and marketing personnel. We may not be able to accomplish these tasks, and our failure to accomplish any of them could prevent us from successfully growing our company.

Enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize Gimoti and affect the prices we may obtain.

In the United States and some foreign jurisdictions, there have been, and we expect there will continue to be, a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval for Gimoti, restrict or regulate post-approval activities and affect our ability to profitably sell our product candidate, assuming we obtain marketing approval.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We are not sure whether additional legislative changes will be enacted, or whether FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of Gimoti, if any, may be. In addition, increased scrutiny by the U.S. Congress of FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

In 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the Affordable Care Act, was signed into law. The Affordable Care Act was intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. The Affordable Care Act, among other things, increased the Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program for both branded and generic drugs and revised the definition of "average manufacturer price" for reporting purposes, which could further increase the amount of Medicaid drug rebates to states. Further, the law imposes a significant annual fee on companies that manufacture or import branded prescription drug products, increased the number of entities eligible for discounts under the 340B program and included a discount on brand name drugs for Medicare Part D beneficiaries in the coverage gap, or "donut hole." Substantial provisions affecting compliance have also been enacted, which may require us to modify our business practices with healthcare practitioners.

Since its enactment, there have been judicial and Congressional challenges to certain aspects of the Affordable Care Act. We expect that the current administration and U.S. Congress may seek to modify, repeal, or otherwise invalidate all, or certain provisions of, the Affordable Care Act. For example, the Tax Cuts and Jobs Act, or Tax Act, was enacted, which, among other things, removes penalties for not complying with Affordable Care Act's individual mandate to carry health insurance. On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, ruled that the individual mandate is a critical and inseverable feature of the Affordable Care Act, and therefore, because it was repealed as part of the Tax Act, the remaining provisions of the Affordable Care Act are invalid as well. While the Trump Administration and the Centers for Medicare & Medicaid Services have both stated that the

ruling will have no immediate effect, it is unclear how this decision, subsequent appeals, if any, will impact the law. Additionally, there is still uncertainty with respect to the impact President Trump's administration and the U.S. Congress may have, if any, and any changes will likely take time to unfold, and could have an impact on coverage and reimbursement for healthcare items and services covered by plans that were authorized by the Affordable Care Act. However, we cannot predict the ultimate content, timing or effect of any healthcare reform legislation or the impact of potential legislation on us.

In addition, other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. These changes include aggregate reductions to Medicare payments to providers of two percent per fiscal year, which went into effect on April 1, 2013, and due to subsequent legislative amendments, will remain in effect through 2027, unless additional Congressional action is taken and the American Taxpayer Relief Act of 2012 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. Recently there has also been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted legislation designed to, among other things, reform government program reimbursement methodologies. Individual states in the United States have also become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. These laws and the regulations and policies implementing them, as well

as other healthcare reform measures that may be adopted in the future, may have a material adverse effect on our industry generally and on our ability to successfully develop and commercialize our products, if approved.

If we or our commercialization partners market products in a manner that violates healthcare laws, we may be subject to civil or criminal penalties.

In addition to FDA restrictions on marketing of pharmaceutical products, several other types of state and federal healthcare fraud and abuse laws have been applied in recent years to restrict business activities in the pharmaceutical industry, including certain marketing practices. These laws include false claims, anti-kickback, data privacy and security and physician payment transparency laws and regulations. Because of the breadth of these laws and the narrowness of the safe harbors, it is possible that some of our business activities could be subject to challenge under one or more of these laws.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce, or in return for, purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other. Although there are several statutory exceptions and regulatory safe harbors protecting certain common activities from prosecution, the exceptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exception or safe harbor. Our practices may not in all cases meet all of the criteria for safe harbor protection from anti-kickback liability. Further, the Affordable Care Act, among other things, amends the intent requirement of the federal Anti-Kickback Statute and the criminal healthcare fraud statutes that prohibit executing a scheme to defraud any federal healthcare benefit program or making false statements relating to healthcare matters. A person or entity no longer needs to have actual knowledge of these statutes or specific intent to violate them in order to have committed a violation. In addition, the Affordable Care Act provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act.

Federal civil and criminal false claims laws, including the False Claims Act, prohibit any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, or causing to be made, a false statement to get a false claim paid. Violations of the False Claims Act can result in very significant monetary penalties and treble damages. Over the past few years, several pharmaceutical and other healthcare companies have been prosecuted under these laws for a variety of alleged promotional and marketing activities, such as: allegedly providing free trips, free goods, sham consulting fees and grants and other monetary benefits to prescribers; reporting to pricing services inflated average wholesale prices that were then used by federal programs to set reimbursement rates; engaging in off-label promotion that caused claims to be submitted to Medicaid for non-covered, off-label uses; and submitting inflated best price information to the Medicaid Rebate Program to reduce liability for Medicaid rebates. Most states also have statutes or regulations similar to the federal anti-kickback law and false claims laws, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

Federal civil monetary penalties laws impose civil fines for, among other things, the offering or transfer of remuneration to a Medicare or state healthcare program beneficiary if the person knows or should know it is likely to influence the beneficiary’s selection of a particular provider, practitioner, or supplier of services reimbursable by Medicare or a state healthcare program, unless an exception applies.

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. Like the federal Anti-Kickback Statute, the Affordable Care Act amended the intent standard for certain healthcare fraud under HIPAA such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

Federal price reporting laws require manufactures to calculate and report complex pricing metrics to government programs, where such reported prices may be used in the calculation of reimbursement and/or discounts on approved products.

Federal and state consumer protection and unfair competition laws broadly regulate marketplace activities and activities that potentially harm consumers.

Once our products are approved and we commence sales in the United States, we will also be required to comply with the federal Physician Payment Sunshine Act, which requires manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children’s Health Insurance Program (with certain exceptions) to report annually to the government information related to payments or other “transfers of value” made to physicians (defined to include doctors, dentists,

optometrists, podiatrists and chiropractors) and teaching hospitals, and applicable manufacturers and group purchasing organizations to report annually to the government ownership and investment interests held by physicians (as defined above) and their immediate family members. Manufacturers are required to report such data to the government by the 90th calendar day of each year. There are also several states with similar laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures and pricing information, and/or require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by HITECH and its implementing regulations, imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's security standards directly applicable to business associates, independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also created four new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, 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 attorneys' fees and costs associated with pursuing federal civil actions.

Similar healthcare laws and regulations exist in the European Union and other jurisdictions, including reporting requirements detailing interactions with and payments to healthcare providers and requirements regarding the collection, distribution, use, security, and storage of personally identifiable information and other data relating to individuals (including the EU General Data Protection Regulation 2016/679).

The risk of our being found in violation of these laws and regulations is increased by the fact that many of them have not been fully interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. If our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from governmental health care programs, a corporate integrity agreement or other agreement to resolve allegations of non-compliance, individual imprisonment, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our financial results.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of Gimoti.

We face an inherent risk of product liability as a result of the clinical testing of Gimoti and will face an even greater risk if we commercialize the product candidate. For example, we may be sued if Gimoti allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product candidate, negligence, strict liability and a breach of warranties. Claims could also be asserted under state consumer protection acts.

In particular, products containing metoclopramide have been reported to cause side effects, including TD. It is possible that a patient taking Gimoti will be found to experience a variety of side effects. In 2009, FDA required a boxed warning on all metoclopramide product labels concerning the chance of TD for patients taking these products. We expect that the label for Gimoti, if approved, will likely contain a similar warning regarding TD. Several manufactures of metoclopramide products have been sued by patients regarding TD.

If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidate. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for Gimoti;
- injury to our reputation;
- withdrawal of clinical trial participants;
- costs to defend the related litigation;
- a diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- the inability to commercialize Gimoti; and

- a decline in our stock price.

We may form strategic alliances in the future, and we may not realize the benefits of such alliances.

We may form strategic alliances, create joint ventures or collaborations or enter into licensing arrangements with third parties that we believe will complement or augment our existing business, including for the continued development or commercialization of Gimoti. These relationships or those like them may require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our existing stockholders or disrupt our management and business. In addition, we face significant competition in seeking appropriate strategic partners and the negotiation process is time-consuming and complex. Moreover, we may not be successful in our efforts to establish a strategic partnership or other alternative arrangements for Gimoti because third parties may view the development or commercialization risk of Gimoti as too significant or the commercial opportunity for our product candidate as too limited. We cannot be certain that, following a strategic transaction or license, we will achieve the revenues or specific net income that justifies such transaction.

Our business and operations would suffer in the event of system failures, including cyberattacks.

Despite the implementation of security measures, our internal computer systems and those of our current and any future CROs and other contractors and consultants and collaborators are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. While we have not experienced any such material system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development program for Gimoti and our business operations. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Likewise, we rely on third parties to manufacture Gimoti and conduct clinical trials, and similar events relating to their computer systems could also have a material adverse effect on our business. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development and commercialization of our product candidate could be delayed, or otherwise adversely affected.

Business disruptions could seriously harm our future revenues and financial condition and increase our costs and expenses.

Our operations could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or manmade disasters or business interruptions, for which we are predominantly self-insured. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses. We rely on third-party manufacturers to produce our Gimoti. Our ability to obtain clinical supplies of Gimoti could be disrupted, if the operations of these suppliers are affected by a man-made or natural disaster or other business interruption. Our operations are located in Solana Beach, California near major earthquake faults and fire zones. The ultimate impact on us, our significant suppliers and our general infrastructure of being located near major earthquake faults and fire zones and being consolidated in certain geographical areas is unknown, but our operations and financial condition could suffer in the event of a major earthquake, fire or other natural disaster.

If we fail to develop and commercialize other product candidates, we may be unable to grow our business.

As part of our growth strategy, we plan to evaluate the development and/or commercialization of other therapies for GI motility disorders. Similar to our initial focus on gastroparesis, we will evaluate opportunities to in-license or acquire other product candidates as well as commercial products to treat patients suffering from predominantly GI disorders, seeking to identify areas of high unmet medical needs with limited treatment options. These other product candidates will require additional, time-consuming development efforts prior to commercial sale, including preclinical studies, extensive clinical trials and approval by FDA and applicable foreign regulatory authorities. All product

candidates are prone to the risks of failure that are inherent in pharmaceutical product development, including the possibility that the drug candidate will not be shown to be sufficiently safe and/or effective for approval by regulatory authorities. In addition, we cannot assure you that any such products that are approved will be manufactured or produced economically, successfully commercialized or widely accepted in the marketplace or be more effective than other commercially available alternatives.

If we engage in an acquisition, reorganization or business combination, we will incur a variety of risks that could adversely affect our business operations or our stockholders.

From time to time we have considered, and we will continue to consider in the future, strategic business initiatives intended to further the development of our business. These initiatives may include acquiring businesses, technologies or products or entering into a business combination with another company. If we do pursue such a strategy, we could, among other things:

- issue equity securities that would dilute our current stockholders' percentage ownership;
- incur substantial debt that may place strains on our operations;

- spend substantial operational, financial and management resources in integrating new businesses, technologies and products; and
- assume substantial actual or contingent liabilities.

We may be unable to maintain sufficient product liability insurance.

Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of products we develop. We currently carry product liability insurance covering our clinical studies. Although we maintain such insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. If we determine that it is prudent to increase our product liability coverage due to the commercial launch of any product, we may be unable to obtain such increased coverage on acceptable terms or at all. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

Risks Relating to Our Intellectual Property

It is difficult and costly to protect our intellectual property rights, and we cannot ensure the protection of these rights. Any impairment of our intellectual property rights may materially affect our business.

We place considerable importance on obtaining patent protection for new technologies, products and processes because our commercial success will depend, in large part, on obtaining patent protection for new technologies, products and processes, successfully defending these patents against third-party challenges and successfully enforcing our patents against third-party competitors. To that end, we have acquired and will file applications for patents covering formulations containing or uses of Gimoti or our proprietary processes as well as other intellectual property important to our business. One of our patent families related to Gimoti was acquired from Questcor. The method of use patents in this patent family were not written by us or our attorneys, and we did not have control over the drafting and prosecution of these patents. Further, Questcor and other predecessors might not have given the same attention to the drafting and prosecution of these patents as we would have if we had been the owners of the patents and application and had control over the drafting and prosecution.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain and involves complex legal and factual questions for which legal principles remain unresolved. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our technology or products or which effectively prevent others from commercializing competitive technologies and products. In recent years patent rights have been the subject of significant litigation, in particular due to inter partes review, introduced by the America Invents Act of 2012, which allows for quicker patent challenges decided by the U.S. Patent and Trademark Office’s Patent Trial and Appeal Board rather than a lay jury. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. The laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we or our predecessors were the first to make the inventions claimed in our owned and licensed patents or pending patent applications, or that we or our predecessors were the first to file for patent protection of such inventions One or more of these factors could possibly result in findings of invalidity or unenforceability of one or more of the patents we own.

With respect to challenges to the validity of our patents, for example, there might be invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of

invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on a product candidate. Even if a defendant does not prevail on a legal assertion of invalidity and/or unenforceability, our patent claims may be construed in a manner that would limit our ability to enforce such claims against the defendant and others. The cost of defending such a challenge, particularly in a foreign jurisdiction, and any resulting loss of patent protection could have a material adverse impact on one or more of our product candidates and our business.

Enforcing our intellectual property rights against third parties may also cause such third parties to file other counterclaims against us, which could be costly to defend, particularly in a foreign jurisdiction, and could require us to pay substantial damages, cease the sale of certain products or enter into a license agreement and pay royalties (which may not be possible on commercially reasonable terms or at all). Any efforts to enforce our intellectual property rights are also likely to be costly and may divert the efforts of our scientific and management personnel.

The patent rights we own covering Gimoti are directed to specific methods of use and formulations of metoclopramide. As a result, our ability to prevent others from marketing products related to Gimoti may be limited by the lack of patent protection for the active ingredient itself and other metoclopramide formulations may be developed by competitors. The active ingredient in Gimoti is

metoclopramide. No patent protection is available for metoclopramide itself. As a result, competitors who develop and receive required regulatory approval for competing products using the same active ingredient as Gimoti may market their competing products so long as they do not infringe any of the method or formulation patents owned by us.

Third parties may seek approval to market their own products similar to or otherwise competitive with our product candidates. In these circumstances, we may need to defend or assert our patents, including by filing lawsuits alleging patent infringement. The outcome following legal assertions of invalidity and unenforceability is unpredictable. In any of these types of proceedings, a court or agency with jurisdiction may find our patents invalid or unenforceable. Even if we have valid and enforceable patents, these patents still may not provide protection against competing products or processes sufficient to achieve our business objectives. Even after they have issued, our patents and any patents that we license may be challenged, narrowed, invalidated or circumvented. If our patents are invalidated or otherwise limited or will expire prior to the commercialization of our product candidates, other companies may be better able to develop products that compete with ours, which could adversely affect our competitive business position, business prospects and financial condition. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates. The following are examples of litigation and other adversarial proceedings or disputes that we could become a party to involving our patents or patents licensed to us:

- we may initiate litigation or other proceedings against third parties to enforce our patent and trade secret rights;
- third parties may initiate litigation or other proceedings seeking to invalidate patents owned by or licensed to us or to obtain a declaratory judgment that their product or technology does not infringe our patents or patents licensed to us;
- third parties may initiate opposition or reexamination proceedings challenging the validity or scope of our patent rights, requiring us to participate in such proceedings to defend the validity and scope of our patents;