Evoke Pharma Inc
Form 10-K
March 25, 2014
Table of Contents

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, DC 20549

Form 10-K

(Mark One)

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

For the fiscal year ended December 31, 2013

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.)**
505 Lomas Santa Fe Drive, Suite 270	
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 x

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 x

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 x No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). x Yes ¨ No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of 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 or a smaller reporting company. See definitions of large accelerated filer , accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ¨	Accelerated filer ¨
Non-accelerated filer ¨	Smaller reporting company x

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 x

As of March 20, 2014, the aggregate market value of the registrant s common stock held by non-affiliates of the registrant was approximately $27,627,705, based on the closing price of the registrant s common stock on the NASDAQ Capital Market of $10.34 per share.

The number of outstanding shares of the registrant s common stock, par value $0.0001 per share, as of March 20, 2014 was 6,099,547.

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 2014 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, 2013.

Table of Contents

EVOKE PHARMA, INC.

FORM 10-K ANNUAL REPORT

For the Fiscal Year Ended December 31, 2013

Table of Contents

Table of Contents

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, 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, anticipate, could, intend, target, projec believes, estimates, predicts, potential or continue or the negative of these 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 EVK-001, including data regarding the estimated size of those markets, their projected growth rates, the incidence of certain medical conditions, statements that certain drugs, 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, 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 ref 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 EVK-001, a metoclopramide nasal spray for the relief of symptoms associated with acute and recurrent diabetic gastroparesis in women with diabetes mellitus. Diabetic gastroparesis is a GI disorder afflicting millions of sufferers worldwide in which the stomach takes too long to empty its contents resulting in serious digestive system symptoms. Metoclopramide is the only product currently approved in the United States to treat gastroparesis, and is currently available only in oral and intravenous forms. EVK-001 is a novel formulation of this drug, designed to provide systemic delivery of metoclopramide through intranasal administration.

Gastroparesis is a condition of delayed gastric emptying in the absence of mechanical obstruction. Gastroparesis results in food remaining in the stomach for a longer time than normal, yielding a variety of symptoms. Gastroparesis is a common problem in individuals with diabetes, but also is observed in patients with prior gastric surgery, a preceding infectious illness, pseudo-obstruction, collagen vascular disorders and anorexia nervosa. 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. Symptoms of gastroparesis include nausea, vomiting, abdominal pain, bloating, early satiety, lack of appetite, and weight loss. The disorder can lead to considerable pain and discomfort, poor nutrition, impaired glycemic control and diminished quality of life. According to a 2008 study published in the *American Journal of Gastroenterology*, it is estimated that hospitalization costs associated with gastroparesis exceed $3.5 billion annually.

We believe intranasal administration has the potential to offer our target gastroparesis patients a preferred treatment option because, unlike oral metoclopramide which might be delayed in absorption due to gastroparesis itself, EVK-001 is designed to effectively bypass the digestive system and allow for more predictable drug administration across the thin mucosa in the nasal cavity. For patients suffering from nausea and vomiting who might not be able to absorb therapeutics via oral delivery, EVK-001 is designed to allow for rapid and predictable drug administration through the nasal route.

Table of Contents

We have evaluated EVK-001 in a multicenter, randomized, double-blind, placebo-controlled parallel group, dose-ranging Phase 2b clinical trial in 287 patients with diabetic gastroparesis where EVK-001 was observed to be effective in improving the most prevalent and clinically relevant symptoms associated with gastroparesis in women while exhibiting a favorable safety profile. We plan to initiate a Phase 3 trial of EVK-001 in female patients with symptoms associated with acute and recurrent diabetic gastroparesis in the first half of 2014. We anticipate receiving topline data from this trial in mid-2015. We will need to successfully complete this trial, as well as a thorough QT, or TQT, study, which is an evaluation of cardiac safety, before we are able to submit a new drug application, or NDA, to the U.S. Food and Drug Administration, or FDA, for EVK-001. FDA approval of the NDA is required in order for us to commercially market EVK-001 in the United States. In addition, based on our discussions with the FDA, we plan to conduct a similar study for safety and efficacy in male patients with symptoms associated with acute and recurrent diabetic gastroparesis to assess the safety and efficacy of EVK-001 in men. We anticipate this trial will be conducted concurrently with the Phase 3 trial in women. The completion of the male companion trial is not required for submission of the NDA for EVK-001 for women; however, we expect to include safety data from this trial in our NDA submission for EVK-001.

At this time, due to the risks inherent in the drug development process, we are unable to estimate with any certainty the costs we will incur in the continued development of EVK-001 for potential commercialization. However, we currently estimate the costs to complete our Phase 3 clinical trial in women, our companion clinical trial in men and a TQT study of EVK-001 will be approximately $15.0 million.

Business Strategy

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

Continue development and pursue regulatory approval for EVK-001. We are currently preparing to initiate a Phase 3 trial of EVK-001 in female patients suffering from diabetic gastroparesis in the first half of 2014.

Seek partnerships to accelerate and maximize the potential for EVK-001. As we continue to generate data on EVK-001, we will seek partnering opportunities with pharmaceutical companies that have established development and sales and marketing capabilities to potentially enhance and accelerate the development and commercialization of EVK-001.

Explore building in-house capabilities to potentially commercialize EVK-001 in the United States. As EVK-001 progresses through its Phase 3 clinical program, in addition to partnering opportunities, we intend to evaluate the development of our own specialty sales force and marketing capabilities to allow us to directly market EVK-001 in the United States, if approved by the FDA.

Explore regulatory approval of EVK-001 outside the United States. We will initially seek approval of EVK-001 in the United States and 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 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 one of the most common GI disorders. Motility disorders affect the orderly contractions or relaxation of the GI tract which move contents forward and prevent backwards 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 symptoms such as abdominal pain, nausea, vomiting, constipation, diarrhea, bloating, decreased appetite, early satiety, swallowing difficulties, heartburn and/or incontinence.

Table of Contents

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 cease altogether. The following graph depicts the timing associated the emptying of solids in patients with diabetic gastroparesis compared to normal individuals:

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 symptoms that include nausea, vomiting, early satiety, bloating, and abdominal pain. As a result of these symptoms, patients may limit their food and liquid intake leading to poor nutrition and dehydration with the patient 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 severe 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 or 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.

Table of Contents

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; although, 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, forward movement of food through the GI tract is delayed. 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 2011, the American Diabetes Association estimated that diabetes affects approximately 26 million people of all ages in the United States, equating to about 8.3% of the U.S. 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 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 recent 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 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 and intravenous metoclopramide, and the oral disintegrating tablet, or ODT, formulation of metoclopramide (Metozolv® ODT), with approximately 5 million prescriptions in the United

States per year, according to IMS Health. Due to the limited availability of FDA-approved treatments for gastroparesis, physicians 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, domperidone, 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.

EVK-001 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 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 nausea and vomiting.

Our Solution: EVK-001 (Metoclopramide Nasal Spray)

We are developing EVK-001, 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 with diabetes mellitus. Since its approval in 1980, oral and intravenous metoclopramide have been the only products approved in the United States to treat gastroparesis. EVK-001 is a novel formulation of metoclopramide offering systemic delivery by intranasal administration.

We are developing the intranasal formulation of metoclopramide to provide our targeted patients 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. Intranasal 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 blocks or slows the movement of the contents of the stomach to the small intestine, oral drug administration is often compromised. Unlike the oral tablet formulation of metoclopramide, we believe that EVK-001 may be tolerated even when patients are experiencing nausea and vomiting. The intranasal formulation may also provide a predictable and consistent means of delivering metoclopramide in patients with delayed gastric emptying and/or frequent vomiting.

Table of Contents

We believe that if approved EVK-001 could also offer an alternative route of administration for female patients with severe symptoms of diabetic gastroparesis, who typically receive the intravenous formulation of metoclopramide. 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.

Phase 2b Clinical Trial

We have evaluated EVK-001 in a multicenter, randomized, double-blind, placebo-controlled parallel group, dose-ranging Phase 2b clinical trial in 287 subjects (79% female) with diabetic gastroparesis. Subjects in the trial were between the ages of 18 and 75, with a history of diabetes (type I and type II) 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 on the drug or placebo.

In this trial, EVK-001 demonstrated effectiveness in reducing the most common and clinically relevant symptoms associated with gastroparesis in women, while exhibiting a favorable safety profile. EVK-001 was shown to provide a statistically significant clinical benefit as defined by a reduction in the symptoms of gastroparesis as measured by the mGCSI-DD in women (p <0.025). Male subjects treated with EVK-001 showed some improvement in gastroparesis symptoms, but did not show a statistically significant difference compared to placebo. Due to these 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 intravenous). Previous metoclopramide studies enrolled small numbers of subjects and did not evaluate gender. Fewer than 150 subjects were enrolled across all studies included in the NDA for Reglan. The results of the Phase 2b trial are consistent with what is known about 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 EVK-001 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 EVK-001: 10 mg and 14 mg; as well as placebo. The study drug was administered for the 28-day treatment period as a single intranasal 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 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 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 FDA and its Study Endpoint and Labeling Division, these additional symptom data were used to further refine the patient reported outcome instrument. The result is a 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 the intention-to-treat population based 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 EVK-001-treated patients 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 EVK-001 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.

Table of Contents

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 EVK-001 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 EVK-001 compared to placebo in the Phase 2b clinical trial across all subjects and for male and female patients separately.

EVK-001 Phase 2b Clinical Trial

Gastroparesis Study Endpoint Points *P* -Value Summary

(EVK-001 vs. Placebo: Change from Baseline to Week 4)

	EVK-001 10 mg *p*-values	**EVK-001 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 4 symptoms collected on a severity rating scale of 0 to 5. Baseline was 7 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 9 symptoms collected on a severity rating scale of 0 to 5. Baseline was 7 days prior to treatment or qualifying days during washout and Week 4 was days 21 to 27 of treatment.

Table of Contents

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

EVK-001 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 analysis of covariance, or ANCOVA, model with effects for treatment group and baseline value as a covariate

Table of Contents

Phase 2b Safety Observations

In the Phase 2b clinical trial, EVK-001 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 EVK-001 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 2 Subjects in Any Treatment Group

	All Subjects		
System Organ Class Preferred Term	**Placebo (N = 95)**	**EVK-001 10 mg (N = 95)**	**EVK-001 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 EVK-001 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 EVK-001, 20 mg EVK-001, 10 mg oral tablet, and 5 mg/mL 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 intranasal administration of the 10 mg and 20 mg doses of EVK-001, mean plasma metoclopramide concentrations increased in a dose-related manner, as did mean values for C max and AUC (inf). The absolute bioavailability of EVK-001 after intranasal 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 EVK-001 as well as the oral and injection forms.

Table of Contents

EVK-001 Phase 1 Clinical Trial

Mean Plasma Concentrations of Metoclopramide

(15 minute intervals 0-2h)

Prior Development

From 1985 to present, we, or our predecessors, have conducted 24 clinical studies to evaluate the safety and pharmacokinetic profile of nasal spray formulations of metoclopramide in healthy volunteers and the safety, efficacy, pharmacokinetic and pharmacodynamic profile of metoclopramide nasal spray in patients. A total of 1,045 patients have been dosed in these studies with intranasal formulations of metoclopramide at doses ranging from 10 mg to 80 mg. In one study, a Phase 2, multicenter, randomized, open-label, parallel design study, Questcor Pharmaceuticals, Inc., or Questcor, compared the efficacy and safety of two doses of metoclopramide nasal spray, 10 mg and 20 mg, with the 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 EVK-001 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 EVK-001 for patients. We also developed the current formulation with excipients that are at or below the levels listed in the FDA s Inactive Ingredient Database for intranasal products. We evaluated the current formulation of EVK-001 in 329 patients in our completed Phase 1 and Phase 2 clinical trials and intend to evaluate the same formulation in our proposed Phase 3 clinical trial. Similarly, the nasal spray pump used in our completed Phase 1 and Phase 2 clinical trials was identical and will also be used in our proposed Phase 3 clinical trial.

The primary container closure system for EVK-001 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.

Our Planned Four-Week Phase 3 Clinical Trial in Female Subjects with Diabetic Gastroparesis

Based on discussions with the FDA, we plan to conduct one Phase 3 trial in women, which we believe, if successful, will be sufficient for NDA submission. We plan to initiate the four-week, multicenter, randomized, double-blind, placebo-controlled, parallel Phase 3 clinical trial to evaluate the efficacy, safety and population pharmacokinetics of EVK-001 in adult female subjects with diabetic gastroparesis in the first half of 2014. We plan to enroll approximately 200 patients at approximately 60 sites across the United States. The trial population will consist of female diabetic patients with gastroparesis, identified by the presence of relevant symptoms and delayed gastric emptying. Female subjects with diabetic gastroparesis meeting the protocol-specified entry criteria will be studied in a parallel-group design with randomization in a 1:1 ratio to EVK-001 10 mg or placebo administered as a single intranasal spray four times daily; 30 minutes before meals and at bedtime.

Based on our discussions with the FDA, we plan to use specific symptoms from a composite score, the Gastroparesis Symptom Assessment, or GSA, as a patient-reported outcomes instrument to assess efficacy in this patient population. The primary efficacy endpoint for this Phase 3 clinical trial will be based upon a change from baseline in total composite score of the specific symptoms included in the GSA. We anticipate receiving topline data from this trial in mid-2015. Also based on discussions with FDA, and to assess safety in men, we plan to conduct a similar and concurrent companion study for safety and efficacy in diabetic men with gastroparesis. The trial design will include an early stop for futility. The FDA has indicated that completion of the male companion study is not required for submission of the NDA seeking approval of EVK-001 for use in women. Whether the male study stops early for futility or continues to enroll, we plan to include safety data from the male companion study in the NDA seeking approval for the drug for use in women. We also plan to conduct the required TQT study of EVK-001 prior to NDA submission.

Table of Contents

Intellectual Property and Proprietary Rights

Overview

We are building an intellectual property portfolio for EVK-001 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 success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for the technologies we consider important to our business, defend our patents, preserve the confidentiality of our trade secrets and operate our business without infringing the patents and proprietary rights of third parties.

Patent Portfolio

Our patent portfolio currently includes the following patents and applications:

U.S. Patent 6,770,262 Nasal Administration of Agents for the Treatment of Gastroparesis. This patent expires in 2021.

U.S. Patent 5,760,086 Nasal Administration for the Treatment of Delayed Onset Emesis. This patent expires in 2016.

U.S. Patent 8,334,281 Nasal Formulations of Metoclopramide. This patent expires in 2030.

Non-Provisional Patent Application No. PCT/US2012/052096 Treatment of Symptoms of Associated with Female Gastroparesis. If granted, this patent would expire in 2032.

We have also been granted patents in the European Union for the method of use of metoclopramide via nasal delivery for gastroparesis. These patents provide protection through 2021. We have also received patents in the European Union covering the intranasal use of metoclopramide for delayed onset emesis. These patents offer protection through 2016.

The United States patent system permits the filing of provisional and non-provisional patent applications. A non-provisional patent application is examined by the U.S. Patent and Trademark Office, or USPTO, and can mature into a patent once the USPTO determines that the claimed invention meets the standards for patentability. A provisional patent application is not examined for patentability, and automatically expires 12 months after its filing date. As a result, a provisional patent application cannot mature into a patent. The requirements for filing a provisional patent application are not as strict as those for filing a non-provisional patent application. Provisional applications are

often used, among other things, to establish an earlier filing date for a subsequent non-provisional patent application. The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application. In the United States, a patent s term may be lengthened by patent term adjustment, or PTA, which compensates a patentee for administrative delays by the USPTO in granting a patent. In view of a recent court decision, the USPTO is under greater scrutiny regarding its calculations where the USPTO erred in calculating the patent term adjustment for the patents in question denying the patentee a portion of the patent term to which it was entitled. Alternatively, a patent s term may be shortened if