CORCEPT THERAPEUTICS INC
Form 10-K
March 15, 2013
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

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

For the fiscal year ended December 31, 2012

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: 000-50679

CORCEPT THERAPEUTICS INCORPORATED

(Exact Name of Corporation as Specified in Its Charter)

Delaware	**77-0487658**
(State or other jurisdiction of incorporation or organization)	*(I.R.S. Employer Identification No.)*

149 Commonwealth Drive

Menlo Park, CA 94025

(Address of principal executive offices) (zip code)

(650) 327-3270

(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, $0.001 par value	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 Section 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). Yes x 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 to 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 the definitions of large accelerated filer , accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act.

Large accelerated filer ¨ Accelerated filer x
Non-accelerated filer ¨ (Do not check if a smaller reporting company) Smaller reporting company ¨
Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ¨ No x

The aggregate market value of voting and non-voting common equity held by non-affiliates of the Registrant was $241,382,000 as of June 30, 2012 based upon the closing price on the NASDAQ Capital Market reported for such date. This calculation does not reflect a determination that certain persons are affiliates of the Registrant for any other purpose.

On March 1, 2013 there were 99,814,250 shares of common stock outstanding at a par value of $0.001 per share.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant s definitive proxy statement for its 2013 Annual Meeting of Stockholders are incorporated by reference in Items 10, 11, 12, 13 and 14 of Part III.

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Form 10-K

For the year ended December 31, 2012

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PART I

This Annual Report on Form 10-K (Form 10-K) contains forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended (Exchange Act), and Section 27A of the Securities Act of 1933, as amended (Securities Act). All statements contained in this Form 10-K, other than statements of historical fact, are forward-looking statements. When used in this report or elsewhere by management from time to time, the words believe, anticipate, intend, plan, estimate, expect, may, will, should, seeks and sim forward-looking statements. Such forward-looking statements are based on current expectations, but the absence of these words does not necessarily mean that a statement is not forward-looking. Forward-looking statements made in this Form 10-K include, but are not limited to, statements about:

- *our ability to manufacture, market and sell Korlym (mifepristone) 300mg Tablets;*
- *our ability to realize the benefits of Orphan Drug Designation of Korlym in the United States;*
- *the progress and timing of our research, development and clinical programs and the timing of regulatory activities for mifepristone for the treatment of the psychotic features of psychotic depression;*
- *our estimates regarding enrollment in and the dates by which we expect to report results of our clinical trials and the anticipated results of these trials;*
- *our ability to achieve marketing approval of Korlym in the European Union (EU) and realize the benefits of Orphan Drug Designation there;*
- *the timing of the market introduction of future product candidates, including any compound in our families of selective GR-II antagonists;*
- *our ability to manufacture, market, commercialize and achieve market acceptance for our future product candidates, including mifepristone for the treatment of the psychotic features of psychotic depression and any compound in our families of selective GR-II antagonists;*
- *uncertainties associated with obtaining and enforcing patents;*
- *our estimates for future performance, including revenue and profits; and*
- *our estimates regarding our capital requirements.*

Forward-looking statements are not guarantees of future performance and involve risks and uncertainties. Actual events or results may differ materially from those discussed in the forward-looking statements as a result of various factors. For a more detailed discussion of such forward-looking statements and the potential risks and uncertainties that may impact upon their accuracy, see the Risk Factors section of this Form 10-K and the Overview and Liquidity and Capital Resources sections of the Management s Discussion and Analysis of Financial Condition and Results of Operations section of this Form 10-K. These forward-looking statements reflect our view only as of the date of this report. Except as required by law, we undertake no obligations to update any forward-looking statements. Accordingly, you should also carefully consider the factors set forth in other reports or documents that we file from time to time with the Securities and Exchange Commission (SEC).

ITEM 1. BUSINESS

Overview

We are a pharmaceutical company engaged in the discovery, development and commercialization of drugs for the treatment of severe metabolic and psychiatric disorders. Our focus is on those disorders that are associated with a steroid hormone called cortisol. Elevated levels and abnormal release patterns of cortisol have been implicated in a broad range of human disorders. Since our inception in May 1998, we have been developing mifepristone a potent glucocorticoid receptor II (GR-II) antagonist that blocks the activity of cortisol for the treatment of a number of severe metabolic and psychiatric disorders. We have also discovered three series of novel selective GR-II antagonists and have moved a compound from one of these series into clinical development.

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On February 17, 2012, the United States Food and Drug Administration (FDA) approved Korlym (mifepristone) 300 mg Tablets as a once-daily oral medication for treatment of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing s syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery. FDA approval means that we can market the drug for the approved indication in the United States. We made Korlym available to patients in April 2012 and continue to develop the sales, marketing, medical affairs and logistical infrastructure needed to commercialize the drug. We also have an on-going Phase 3 study of mifepristone, the active ingredient in Korlym, for the psychotic features of psychotic depression.

Unless otherwise stated, all references in this document to we, us, our, Corcept, the Company, our company and similar designations Corcept Therapeutics Incorporated.

Cushing s Syndrome. Cushing s syndrome is a disorder caused by prolonged exposure of the body s tissues to high levels of the hormone cortisol. Sometimes called hypercortisolism, it is relatively uncommon and most often affects adults aged 20 to 50. An estimated 10 to 15 of every one million people are newly diagnosed with this syndrome each year, resulting in approximately 3,000 new patients and an estimated prevalence of 20,000 patients with Cushing s syndrome in the United States.

We received Orphan Drug Designation from the FDA in July 2007 for Korlym for the treatment of endogenous Cushing s syndrome. In the United States, Orphan Drug Designation is a special status granted by the FDA to encourage the development of treatments for diseases or conditions that affect fewer than 200,000 patients. Drugs that receive Orphan Drug Designation obtain seven years of marketing exclusivity for the approved indication from the date of drug approval, as well as tax credits for clinical trial costs, marketing application filing fee waivers and assistance from the FDA in the drug development process.

In October 2011 we received Orphan Drug Designation in the EU. Orphan Drug Designation in the EU confers benefits similar to those in the U.S., but includes ten years of marketing exclusivity for the approved indication in all 27 member states, free scientific advice during drug development, access to a centralized review process and a reduction or complete waiver of fees levied by the European Medicines Agency (EMA). We are working with the EMA now to prepare a Marketing Authorization Application (MAA) that, subject to filing with and review by the EMA, could serve as the basis for Korlym s approval in the EU.

As discussed above, in February 2012, the FDA approved our New Drug Application (NDA) for Korlym as a once-daily oral medication for treatment of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing s syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

Psychotic Depression. We are also developing mifepristone, Korlym s active ingredient, for treatment of the psychotic features of psychotic depression under an exclusive patent license from Stanford University. The FDA has granted fast track status to evaluate the safety and efficacy of mifepristone for the treatment of the psychotic features of psychotic depression.

In March 2008, we began enrollment in Study 14, our ongoing Phase 3 trial in psychotic depression. The protocol for this trial incorporates what we have learned from our three previously completed Phase 3 trials. It attempts to address the established relationship between increased drug plasma levels and clinical response and attempts to decrease the random variability observed in the results of the psychometric instruments used to measure efficacy. In one of the previously completed Phase 3 trials, Study 06, we prospectively tested and confirmed that patients whose plasma levels rose above a predetermined threshold statistically separated from both those patients whose plasma levels were below the threshold and those patients who received placebo; this threshold was established from data produced in earlier studies.

As expected, the group of patients who took 1200 milligrams (mg) of mifepristone in Study 06 developed higher drug plasma levels than did the groups of patients who received lower doses. Further, there was no

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discernible difference in the incidence of adverse events between patients who received placebo in Study 06 and those who received 300 mg, 600 mg or 1200 mg of mifepristone in that study. In August 2011, we published our analysis of these data in *The Journal of Clinical Psychopharmacology*. Based on this information, we are using a mifepristone dose of 1200 mg once per day for seven days in Study 14.

In addition, we are utilizing a third party centralized rating service to independently evaluate patients for entry into the study as well as to evaluate their level of response throughout their participation. We believe the centralization of this process will improve the consistency of rating across clinical trial sites and reduce the background noise that was experienced in earlier studies and is endemic to psychopharmacologic studies. We believe that this change in dose, as well as the other modifications to the protocol, should allow us to demonstrate the efficacy of mifepristone in the treatment of the psychotic symptoms of psychotic depression. In mid-2009, in order to conserve financial resources, we reduced the number of clinical sites to eight and extended the timeline for the study s completion. To increase the pace of patient enrollment, we began adding clinical sites in the fourth quarter of 2012 and plan to have 20 clinical sites participating by the end of the first quarter of 2013. Our goal is to enroll a sufficient number of patients by the end of 2013 to be able to perform a successful interim analysis.

Antipsychotic-induced Weight Gain Mitigation. In 2005, we published the results of studies in rats that demonstrated that mifepristone both reversed the weight gain associated with the ongoing use of olanzapine and mitigated the weight gain associated with the initiation of treatment with olanzapine (the active ingredient in Zyprexa®). The results from this study were published in the journal *Brain Behavioral Research* in early 2006. The study was paid for by Eli Lilly and Company (Eli Lilly).

During 2007 we announced positive results from our clinical proof-of-concept study in lean healthy male volunteers evaluating the ability of mifepristone to mitigate weight gain associated with the use of Zyprexa. The results show a statistically significant reduction in weight gain in those subjects who took Zyprexa plus mifepristone compared to those who took Zyprexa plus placebo. Also, the addition of mifepristone to treatment with Zyprexa had a beneficial impact on secondary metabolic measures such as fasting insulin, triglycerides and abdominal fat, as indicated by waist circumference. Eli Lilly provided Zyprexa and financial support for this study and its results were published in the journal *Advances in Therapy* in 2009. In January 2009, we announced positive results from a similar proof-of-concept study evaluating the ability of mifepristone to mitigate weight gain associated with the use of Johnson & Johnson s Risperdal®. This study confirmed and extended the earlier results seen with mifepristone and Zyprexa, demonstrating a statistically significant reduction in weight and secondary metabolic endpoints of fasting insulin, triglycerides and abdominal fat, as indicated by waist circumference. The results from the study of mifepristone and Risperdal were presented at several scientific conferences, including the American Diabetes Association meeting in June 2009, and were published in the journal *Obesity* in 2010.

The combination of Zyprexa or Risperdal and mifepristone is not approved for any indication. The purpose of these studies was to explore the hypothesis that GR-II antagonists, such as mifepristone and our next generation of selective GR-II antagonists, would mitigate weight gain associated with antipsychotic medications. The group of medications known as second generation antipsychotic medication, including Zyprexa, Risperdal, Clozaril® and Seroquel®, are widely used to treat schizophrenia and bipolar disorder. All medications in this group are associated with treatment-emergent weight gain of varying degrees and carry a warning in their labels relating to treatment-emergent hyperglycemia and diabetes mellitus.

Selective GR-II Receptor Antagonists. In 2003, we initiated a discovery research program to identify and patent selective GR-II antagonists. Our intent is to develop a pipeline of products for proprietary use. Three distinct series of selective GR-II antagonists have been identified. These compounds, like the active ingredient in our lead product Korlym, potently block the cortisol receptor (GR-II) but, unlike Korlym, do not appear to block the PR (progesterone), ER (estrogen), AR (androgen) or GR-I (mineralocorticoid) receptors. Both the United

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States Patent & Trademark Office (USPTO) and the European Patent Office (EPO) have issued to us composition of matter patents in each of the three series. Two additional composition of matter patent applications are pending. See Business Intellectual Property.

Several of our new compounds have demonstrated positive results in animal models for the prevention and reversal of anti-psychotic-induced weight gain, as well as animal and *in vitro* models of other metabolic and common central nervous system disorders. One of these new compounds, CORT 108297, is in exploratory Phase 2 clinical trials and we plan to explore its potential use in several indications. *See Business Next-Generation Selective GR-II Antagonists for the Prevention and Reversal of Anti-Psychotic-Induced Weight Gain.* We have identified other selective GR-II antagonists from our proprietary series that we believe may have utility as therapeutic agents in a variety of diseases. We intend to continue our discovery research program with the goal of identifying new selective GR-II antagonists and to perform manufacturing and pre-clinical development on several of these compounds and to submit Investigational New Drug applications (INDs) with respect to the most promising of them, as we deem appropriate.

The Role of Cortisol in Disease

Cortisol is a steroid hormone that plays a significant role in the way the body reacts to stressful conditions and is essential for survival. Cortisol significantly influences metabolism, exerts a clinically useful anti-inflammatory effect and contributes to emotional stability. Insufficient levels of cortisol may lead to dehydration, hypotension, shock, fatigue, low resistance to infection, trauma, stress and hypoglycemia. Excessive levels of cortisol may lead to impaired glucose tolerance, diabetes, obesity, depressed mood, psychosis, wasting of the arms and legs, edema, fatigue, hypertension, and other problems.

Elevated levels and abnormal release patterns of cortisol have also been linked to a broad range of metabolic and psychiatric conditions, such as weight gain, diabetes, hypertension, mood changes, psychosis and cognitive impairment.

While excess cortisol may play a role in numerous diseases, Cushing s syndrome (sometimes called hypercortisolism) is the archetypal disease of excess cortisol, as Cushing s syndrome patients have tumors that produce excess levels of cortisol or adrenocorticotropic hormone (ACTH), which stimulates the production of cortisol. Exposure to high levels of cortisol can result in weight gain, diabetes, hypertension, infections, severe fatigue and psychosis.

Many studies have shown that patients with psychotic depression have elevated levels and abnormal release patterns of cortisol. This abnormal cortisol activity is not usually present in patients with nonpsychotic depression. More than 20 years ago, one of our scientific co-founders postulated that elevated levels of cortisol in patients with psychotic depression lead to elevated levels of dopamine, an important chemical substance found in the brain. Elevated levels of dopamine have been implicated in both delusional thinking and hallucinations. This hypothesis led to the concept that, by regulating the level and release patterns of cortisol, one could normalize dopamine levels in the brain, which may, in turn, ameliorate the symptoms of psychotic depression. In addition to cortisol s effect on dopamine levels, research has shown that prolonged elevated cortisol may also play a direct role in causing the symptoms of psychotic depression.

The challenge in regulating levels of cortisol is that cortisol is needed for natural processes in the human body. Destroying the ability of the body to make cortisol or to drastically reduce its presence would result in serious detrimental effects. To have a viable therapeutic effect, a compound must be able to selectively modulate cortisol s effects.

Glucocorticoid Receptor Antagonists

Cortisol is produced by the adrenal glands and is carried via the bloodstream throughout the body, including to the brain, where it directly influences neuronal function. In the brain, cortisol binds to two receptors,

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Glucocorticoid Receptor I and Glucocorticoid Receptor II, also known as GR-I and GR-II. GR-I is a high-affinity receptor that is involved in the routine functions of cortisol in the brain. It has approximately ten times the affinity of GR-II for cortisol and its binding sites are filled with cortisol nearly all the time. In general, GR-II binding sites do not fill until levels of cortisol become elevated. Short-term activation of GR-II has benefits, which include helping the individual to be more alert and better able to function under stressful conditions. Long-term activation of GR-II, however, has been shown to have significant toxicity and appears to be linked to multiple metabolic and psychiatric disease states, such as Cushing s syndrome and psychotic depression. The action of cortisol can be moderated by the use of blockers, or antagonists, that prevent the binding of the hormone to its receptors. These antagonists, referred to as glucocorticoid or cortisol receptor antagonists, may prevent the undesirable effects of elevated levels and abnormal release patterns of cortisol.

Mifepristone, the active ingredient in Korlym, works by selectively blocking the binding of cortisol to GR-II. It is neither an antagonist nor agonist of GR-I. It also blocks the binding of progesterone to the progesterone receptor (PR). Because of its selective affinity, we believe that mifepristone can have a therapeutic benefit by modulating the effects of abnormal levels and release patterns of cortisol without compromising the necessary normal functions of cortisol. We have also discovered three series of additional compounds that, like mifepristone, potently block the GR-II receptor, but, unlike mifepristone, do not block the progesterone receptor. One of these compounds, CORT 108297, is now being studied in the clinic. We have identified other compounds suitable for advancement and plan to begin pre-clinical work on several of them in 2013.

Overview of Cushing s Syndrome

Endogenous Cushing s syndrome is caused by prolonged exposure of the body s tissues to high levels of the hormone cortisol produced by a tumor or tumors. In endogenous Cushing s syndrome, the excess cortisol is stimulated or directly produced by pituitary, adrenal or ectopic tumors. Cushing s syndrome is an orphan indication which most commonly affects adults aged 20 to 50. An estimated 10 to 15 of every one million people are newly diagnosed with this syndrome each year, resulting in approximately 3,000 new patients in the United States. An estimated 20,000 patients in the United States have been diagnosed with Cushing s syndrome. Symptoms vary, but most people have one or more of the following manifestations: high blood sugar, diabetes, high blood pressure, upper body obesity, rounded face, increased fat around the neck, thinning arms and legs, severe fatigue and weak muscles. Irritability, anxiety, cognitive disturbances and depression are also common. Cushing s syndrome can affect every organ system in the body and can be lethal if not treated effectively.

The preferred treatment for Cushing s syndrome patients is surgery, which if successful can cure the disease. Depending on the type of tumor, surgery can result in a range of complications and has varying rates of success. In approximately half of the patients, surgery is not successful, either because the tumor cannot be removed completely or the disease returns.

Commercialization of Korlym

Korlym is the first approved therapy for patients with endogenous Cushing s syndrome. On February 17, 2012, Korlym was approved by the FDA for hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing s syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery. As indicated in the medicine s prescribing information, physicians prescribing Korlym may determine the appropriate dose for each patient by assessing tolerability and degree of improvement in manifestations of Cushing s syndrome. In the first six weeks, these manifestations may include changes in glucose control, anti-diabetic medication requirements, insulin levels and psychiatric symptoms. After two months, assessment may also be based on improvements in cushingoid appearance, acne, hirsutism, striae, decreased body weight, along with further changes in glucose control.

We have begun marketing Korlym in the United States, without a partner, because we believe that the market is highly concentrated and accessible. Following the drug s approval by the FDA in February 2012,

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we began hiring a small number of experienced medical science liaisons (MSLs), supported by medical affairs and other infrastructure, to educate health care providers about Korlym. To reach more physicians, in October 2012 we began deploying a small force of experienced field sales personnel. We intend for our MSLs and sales representatives to focus on patients who are in the care of an endocrinologist and in active treatment for their disease. We estimate that we would need to target approximately 500 endocrinologists to reach a large portion of the Cushing s syndrome population in active treatment. We also reach patients directly through web-based initiatives and interactions with patient groups. We have executed agreements with a specialty pharmacy, a specialty distributor, a contract sales organization, and a third-party logistics company to distribute Korlym and provide logistical support.

A large percentage of the people who suffer from Cushing s syndrome remain undiagnosed or inadequately treated. We intend to develop programs to educate the medical community and patients about early diagnosis of this syndrome and to increase awareness regarding the role of GR-II antagonists for this syndrome. We have retained a vendor to help patients with the reimbursement process. This vendor also administers our financial assistance programs for uninsured or under-insured patients who cannot otherwise afford the cost of Korlym.

Both the FDA and the European Commission have granted Orphan Drug Designation for Korlym. In the United States, Orphan drugs receive seven years of marketing exclusivity for the approved indication from the date of approval, as well as tax credits for clinical trial costs, marketing application filing fee waivers and assistance from the FDA in the drug development process. Benefits of Orphan Drug Designation in the EU are similar to those in the U.S., but include ten years of marketing exclusivity for the approved indication in all 27 member states, free scientific advice during drug development, access to a centralized review process and a reduction or complete waiver of fees levied by the European Medicines Agency (EMA). In 2013, we plan to commence a study of Korlym in pediatric Cushing s syndrome patients. If we complete the study and submit the data to the FDA and EMA pursuant to protocols and within timelines that we may agree upon with these agencies, our Orphan Drug marketing exclusivity period will be extended by six months in the United States and two years in the EU.

Additional Trials and Preclinical Studies

As part of its approval for Korlym, the FDA has required us to study the interactions, if any, between Korlym and ketoconazole, an anti-fungal agent that is sometimes used to treat Cushing s syndrome, although it is not approved by the FDA for that purpose. Further, the FDA has required us to perform a drug utilization study to better characterize the reporting rates of adverse events associated with the long-term use of Korlym. On our own initiative, we conducted a long-term extension study in patients who completed the Phase 3 trial to assess safety of chronic dosing. Upon the approval of Korlym we transitioned study patients to commercial product and terminated the study.

Overview of Psychotic Depression

Psychotic depression is a serious psychiatric disease in which a patient suffers from severe depression accompanied by delusions, hallucinations or both. These psychotic features typically develop after the onset of a depressed mood, but may develop concurrently as well. Once psychotic symptoms occur, they usually reappear with each subsequent depressive episode. Of particular importance, when the patient s mood returns to normal the psychosis also resolves.

Data from the National Institute of Mental Health published in 2005 indicate that depressive disorders affect an estimated 9.5% of adults in the United States, or about 19 million people each year. Of these 19 million people, many published studies show that approximately 15-20%, or about three million people, have psychotic depression. Most patients with psychotic depression suffer their first episode of major depression between the ages of 30 and 40 and the majority will experience more than one episode in their lifetime. People with psychotic depression are approximately 70 times more likely to commit suicide in their lifetime than the general population and often require lengthy and expensive hospital stays.

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Current Treatments for Psychotic Depression

There are two treatment approaches for the psychotic features of psychotic depression currently used by psychiatrists: electroconvulsive therapy (ECT) and combination drug therapy, which is a combination of antidepressant and antipsychotic medication. Neither of these treatments has been approved by the FDA for the psychotic features of psychotic depression and both approaches almost always have a slow onset of action, which may result in lengthy and costly hospitalization. Each of these treatments can have debilitating side effects. Of the two treatments, ECT is generally considered to be more effective.

ECT involves passing an electrical current through the brain until the patient has a seizure. At least 100,000 patients receive ECT each year in the United States, with each patient requiring approximately six to twelve procedures over a period of three to five weeks.

Combination drug therapy is an alternative treatment for the psychotic features of psychotic depression that involves taking antipsychotic drugs such as olanzapine, haloperidol or chlorpromazine in combination with antidepressant drugs, such as fluoxetine, imipramine or venlafaxine. Patients on combination drug therapy often require three weeks or more to show improvement in their symptoms and treatment can take months before the symptoms are resolved entirely. Antipsychotic drugs can cause significant adverse side effects, including weight gain, diabetes, sedation, permanent movement disorders and sexual dysfunction.

Mifepristone for the Psychotic Features of Psychotic Depression

We are developing mifepristone as an oral medication to treat the psychotic features of psychotic depression. As a GR-II antagonist, mifepristone appears to mitigate the effects of the elevated and abnormal release patterns of cortisol in patients suffering from psychotic depression. We intend mifepristone to be a once-daily treatment given to patients with psychotic depression over seven consecutive days in a controlled setting, such as a hospital or physician s office.

We believe that mifepristone may significantly reduce psychotic symptoms of psychotic depression in many patients within one week and allow patients to be more easily maintained on antidepressant therapy alone without the need for ECT or antipsychotic medication. We believe that mifepristone may be superior to currently available treatments because we believe that mifepristone will enable patients with psychotic depression to improve their quality of life more quickly and with fewer side effects than with ECT or combination drug therapy.

Completed Clinical Trials of Mifepristone for Psychotic Depression

We have completed seven prior clinical trials evaluating mifepristone for treatment of the psychotic features of psychotic depression, in addition to our ongoing Phase 3 trial. The trials include three Phase 3 trials conducted from 2004 through 2007, in addition to four earlier stage clinical trials with mifepristone. These completed trials generated important data confirming the safety profile of mifepristone (alone and in combination with commonly prescribed antipsychotic and antidepressant medications), demonstrated positive efficacy trends, and provided insights into the design of future clinical trials which might improve the probability of clinical success.

Completed Phase 3 Clinical Trials. In addition to Phase 1 and 2 studies, we have completed three randomized, double-blind, placebo-controlled Phase 3 clinical trials to further assess the safety and efficacy of mifepristone for the treatment of the psychotic features of psychotic depression. Two of these trials (Study 06 and Study 07) were conducted primarily in the United States. The third trial (Study 09) was conducted in Eastern Europe.

The primary endpoint for Study 06 and Study 07 was the proportion of patients with at least a 50% improvement in the Brief Psychiatric Rating Scale Positive Symptom Subscale (BPRS PSS) at both Day 7 and

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Day 56. The primary endpoint for Study 09 was the proportion of patients with at least a 50% improvement in the BPRS PSS, at both Day 7 and Day 28, with day 56 as a secondary endpoint. Patients must have had at least mild psychotic symptoms (BPRS PSS ³ 12) to enter the studies and were hospitalized if clinically necessary.

Study 07: The first of these trials, which began in September 2004, enrolled 257 patients randomized one-to-one to either treatment or placebo. Patients in the treatment arm received 600 mg of mifepristone once daily for seven days. Patients did not take any antidepressant or antipsychotic medication for at least one week before beginning the seven day treatment period. After the seven days of mifepristone treatment, all patients received antidepressant therapy through Day 56. Treatment with antipsychotic medications or ECT was not allowed at any time during the study.

In this study patients receiving mifepristone did not have a statistically significant difference in response rate at the primary endpoint than did the patients receiving placebo. A retrospective analysis of the data showed that patients achieving drug plasma levels higher than 1800 nanograms per milliliter (ng/ml) had a statistically significant greater response rate than placebo. There was also a statistically significant site by treatment effect in this trial. Among the twenty sites who participated from the trial onset, patients who were given mifepristone had a significantly higher response rate than patients who received placebo. Among the sites added later in the trial, there was no significant difference in response rate between mifepristone and placebo patients. These findings were published in 2009 by *Contemporary Clinical Trials.*

Study 09: This study, which commenced in May 2005, was a randomized, double-blind, placebo-controlled study in which 247 patients were enrolled at sites in Eastern Europe. Patients in the treatment arm received 600 mg of mifepristone once daily for seven days. The primary endpoint was the proportion of patients with at least a 50% improvement in the BPRS PSS score at both Day 7 and Day 28. The study did not demonstrate a significant difference in response between patients receiving mifepristone and patients receiving placebo as measured by the primary endpoint. The results at the two key secondary endpoints of Study 09 also were not statistically significant. Study 09 had an extremely high placebo response rate.

Study 06: This trial began in October 2004, and enrolled 443 patients. These patients were randomly assigned to three active dose groups (300 mg, 600 mg and 1200 mg) or a placebo group, with patients receiving once daily dosing for a period of seven days. The three dosing levels responded to the FDA s request to supplement data on a range of doses to augment the data provided by our open label dose ranging study completed in 2001.

The study did not achieve statistical significance with respect to the primary endpoint. However, there was a statistically significant correlation between plasma levels and clinical outcome achieved during treatment. Response rates for patients whose plasma levels rose above a predetermined threshold of 1661 ng/ml were statistically different than those patients whose plasma levels were below the threshold and those patients who received placebo. Further, the incidence of serious adverse events did not differ between placebo and any of the three mifepristone dose groups. In August 2011, we published an analysis of these results in *The Journal of Clinical Psychopharmacology*.

Ongoing Phase 3 trial Study 14: We believe that the confirmation of a correlation between drug concentration and clinical response, as well as other observations from Study 06 and our two other completed Phase 3 clinical trials, served as a strong basis for the design of our ongoing Phase 3 study, which commenced in March 2008. The protocol for this trial incorporates information learned from the three completed Phase 3 trials in that it addresses the established relationship between increased drug plasma levels and clinical response, and it attempts to decrease the random variability observed in the results of the psychometric instruments used to confirm diagnosis and measure efficacy.

Increased Signal : In this trial we are administering a mifepristone dose of 1200 mg once per day for seven days instead of 600 mg once per day for seven days.

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Decreased Noise : We also are utilizing a third party centralized rating service to independently evaluate the patient s diagnosis prior to entry into the study as well as to assess response. We believe the centralization of this process will improve the accuracy of diagnosis and the consistency of rating across clinical trial sites and reduce the background noise that is endemic to psychopharmacologic studies and clearly visible in our earlier studies.

We believe that these changes in the protocol should allow us to establish the efficacy of mifepristone in the treatment of the psychotic features of psychotic depression. Given the serious nature of psychotic depression, the lack of any approved drugs for the disorder and the data from our first clinical trial, the FDA granted a fast track designation for mifepristone for the treatment of the psychotic features of psychotic depression. In addition, the FDA has indicated that mifepristone will receive a priority review if no other treatment is approved for the psychotic features of psychotic depression at the time we submit our NDA.

Enrollment in Study 14 is ongoing. Our goal is to enroll a sufficient number of patients by the end of 2013 to be able to perform a successful interim analysis. To help reach this goal, we plan to increase the number of clinical sites from eight to approximately 20 by the end of the first quarter of 2013.

*Clinical Trial Agreement*s. Many of our Phase 3 clinical trials are conducted through the use of clinical research organizations (CROs.) At our request, these organizations oversee clinical trials at various institutions to test the safety and efficacy of our product candidates for the targeted indications. Our ongoing Phase 3 clinical trial, Study 14, evaluating mifepristone for the treatment of the psychotic features of psychotic depression is being conducted under an agreement with ICON Clinical Research, LP (ICON). We may terminate this agreement with 60 days notice to ICON, or sooner based on mutual agreement of the parties. In addition, we entered into an agreement with MedAvante, Inc. (MedAvante), in March 2008, to provide the centralized psychiatric diagnosis and rating services for patients being screened and enrolled in Study 14. We may terminate this agreement with 30 days notice to MedAvante.

Discovery Research: Next-Generation Selective GR-II Antagonists

In 2003, we initiated a discovery research program to identify and patent selective GR-II antagonists at a contract research organization in the United Kingdom. Through this program we have identified and filed patent applications for three distinct series of selective GR-II antagonists. These compounds appear to be as potent as our lead product mifepristone in blocking cortisol but, unlike mifepristone, they do not appear to block the progesterone or other steroid receptors. Currently, we are investigating several compounds in our research programs. We plan to submit INDs for such additional compounds as our research indicates may be promising and as we deem appropriate.

We have assembled a patent portfolio covering both a broad range of uses and the composition of our new chemical entities.

We have composition of matter claims on three patent families of novel selective glucocorticoid receptor (GR-II) antagonists. Applications for all three families have been allowed or issued in both the United States and Europe. Two additional composition of matter patent applications are pending in both the United States and Europe.

We also have a portfolio of patents describing the use of drugs that block the GR-II receptor for the treatment of metabolic and psychiatric disorders. In addition to psychotic depression, we own or have exclusively licensed issued patents for the use of GR-II antagonists for treatment and / or prevention of:

- weight gain following treatment with antipsychotic medication;
- mild cognitive impairment;
- stress disorders;
- early dementia, including early Alzheimer s disease;

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delirium;

gastroesophageal reflux disease;

cognitive deterioration in adults with Down s Syndrome;

psychosis associated with cocaine addiction;

catatonia; and

increased therapeutic response to ECT.

See Business Intellectual Property.

Next-Generation Selective GR-II Antagonists for the Prevention and Reversal of Antipsychotic-Induced Weight Gain

In January 2009, we announced results from two preclinical studies of our first next-generation selective GR-II receptor antagonist, CORT 108297, for the prevention and reversal of weight gain caused by olanzapine, a medication marketed by Eli Lilly as Zyprexa. Using the same experimental rat model used previously with mifepristone, the preclinical studies demonstrated that CORT 108297 1) reversed and 2) prevented the weight gain caused by olanzapine in rats. Eli Lilly provided olanzapine and funded the cost of the studies.

In the first of these two studies, seventy-two female rats (n=12 per group) were allowed to eat a normal diet for 56 days. During an induction phase of weight gain (study days 1-34), 12 rats were administered placebo, whereas 48 were administered olanzapine. Animals receiving olanzapine gained significantly more weight than animals receiving placebo (p<.000001). On Day 35, the 48 animals that had received olanzapine during the weight induction phase were randomized (n=12 per group) to receive one of the following regimens: placebo, CORT 108297 (20mg/kg), CORT 108297 (60mg/kg), CORT 108297 (120mg/kg) for the subsequent 21 days. There were robust, statistically significant, differences in weight between the olanzapine plus placebo and olanzapine plus CORT 108297 groups: Animals receiving olanzapine and placebo continued to gain significant body weight from day 35 to 56 (p<.0001) while animals receiving olanzapine plus CORT 108297 (all doses) exhibited significant weight reduction (p<.00001). At the highest dose tested (120 mg/kg), the animals weight returned to levels observed prior to initial olanzapine ingestion. The results of this first study suggest that after significant weight gain from olanzapine has already occurred, CORT 108297 can be introduced while olanzapine is continued and reverse the weight gain caused by olanzapine.

In the second study, rats (n = 96) were dosed with placebo, olanzapine (2.4 mg/kg), or, olanzapine plus CORT 108297 (2, 6, 20, 60, or 120 mg/kg) for 21 days. From baseline to day 21, rats administered olanzapine plus CORT 108297 gained significantly less weight than rats receiving olanzapine and placebo (p <.00001). Larger doses of CORT 108297 were significantly correlated with greater weight reduction (p<.00001). This second study suggests that when CORT 108297 is administered concomitantly with olanzapine, weight gain associated with the use of olanzapine can be prevented or at least attenuated.

These first two studies used dose levels of 20 mg/kg, 60 mg/kg and 120 mg/kg of CORT 108297. The results of these two experiments replicated the findings from previous animal studies of mifepristone, and were also consistent with results from randomized trials conducted in humans. The results were presented at the International Society of Psychoneuroendocrinology and the World Congress of Biological Psychiatry conferences in July 2009 and were published in the peer-reviewed journal, *Diabetes Obesity and Metabolism* in 2010.

A third study in the rat further evaluated the dose response relationship of CORT 108297 in preventing olanzapine induced weight gain with doses from 2 mg/kg to 20 mg/kg.

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At the American Diabetes Association conference in June 2009 there was also a presentation of preclinical data from a study which demonstrated that CORT 108297 suppresses body weight gain and improves insulin sensitivity in healthy mice fed a 60% fat diet and high sucrose liquid. In 2011, these study results were published in the peer-reviewed publication, *The Journal of Nutrition and Metabolism*.

The manufacturing and preclinical development of CORT 108297 began late in 2008 and resulted in the submission of an IND to the FDA in December 2009. Dosing of healthy volunteers in the first Phase 1 study of CORT 108297 was completed in July 2010. This initial study was a single dose escalation study in healthy volunteers. We continue to evaluate CORT 108297 in exploratory Phase 2a studies in models of antipsychotic induced weight gain and changes in biomarkers induced by prednisone, a steroid.

If any of our selective GR-II antagonists prove to mitigate the weight gain and metabolic disturbances associated with the use of antipsychotic medication, they could potentially be of benefit to the millions of people currently taking this important pharmacotherapy.

Proof-of-Concept Studies

Metabolic Disorders

In April 2005, we announced results from two preclinical studies conducted in a rat model of olanzapine-induced weight gain. These studies demonstrated that mifepristone s GR-II antagonist action has the potential to both reverse the weight gain associated with olanzapine and to prevent the weight gain associated with the initiation of treatment with olanzapine, which led to our studies in humans.

In 2007, we announced results of our human clinical proof-of-concept study evaluating the ability of mifepristone to mitigate weight gain associated with the administration of Eli Lilly s Zyprexa (olanzapine). The results indicated a statistically significant reduction in weight gain in those subjects who took Zyprexa plus mifepristone compared to those who took Zyprexa plus placebo. Eli Lilly provided Zyprexa and financial support for this study. During 2009, we announced results from another proof-of-concept study evaluating the ability of mifepristone to mitigate weight gain associated with the administration of Johnson & Johnson s Risperdal (risperidone). The results indicated a statistically significant reduction in weight gain in those subjects who took Risperdal plus mifepristone compared to those who took Risperdal plus placebo. Both Zyprexa and Risperdal are indicated for the treatment of schizophrenia and bipolar disorder.

In the study of mifepristone and Zyprexa, 57 lean, healthy men (body mass index of 25 or less) were randomized to receive either Zyprexa plus placebo (n=22), Zyprexa plus mifepristone (n=24) or mifepristone plus placebo (n=11). This study took place in an institutional setting where daily weights were recorded and a range of metabolic parameters were measured. In the two week study, subjects in the Zyprexa plus placebo group gained an average of 7.0 pounds and subjects in the Zyprexa plus mifepristone group gained an average of 4.4 pounds; which is a statistically significant difference ($p<.001$). Subjects in the mifepristone plus placebo group gained an average of 4.4 pounds. The difference in weight gain trajectory was apparent in the first days of the study, reaching statistical significance during the first week. The increase in waist circumference, a surrogate for abdominal fat, in subjects who received Zyprexa plus placebo was also significantly greater than subjects who received Zyprexa plus mifepristone ($p<.01$). The study was not designed to enroll a sufficient number of patients to have statistical power to detect significant effects on metabolic measures; however, the effect of mifepristone in this model was greater than expected. In addition to the finding about waist circumference, notable additional non-statistically significant group differences were observed. Patients taking Zyprexa plus placebo experienced greater increases from baseline to end of study in both triglycerides and fasting insulin compared to patients taking Zyprexa plus mifepristone. No unexpected study drug related adverse events were observed. These results were published in *Advances in Therapy* in 2009.

In the study of mifepristone and Risperdal, 75 lean, healthy men (body mass index of 23 or less) were randomized to receive either Risperdal plus placebo (n=30), Risperdal plus mifepristone (n=30) or mifepristone plus placebo (n=15). This study also took place in an institutional setting where daily weights were recorded and

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a range of metabolic parameters were measured. In this four-week randomized double-blind controlled study, subjects in the Risperdal plus placebo group gained an average of 9.2 pounds, compared to a gain of 5.1 pounds in the Risperdal plus mifepristone group. This difference was statistically significant ($p<0.0001$). Additional important metabolic parameters, including fasting insulin, triglycerides and abdominal fat, as reflected by waist circumference, were also measured. The addition of mifepristone to Risperdal resulted in a statistically significant reduction in fasting insulin levels, triglyceride levels, and abdominal fat (as measured by waist circumference). Consistent with prior studies, mifepristone appeared to be well tolerated. These results were published in *Obesity* in 2010.

The combinations of Zyprexa and mifepristone or Risperdal and mifepristone are not approved for any indication. The purpose of these studies was to explore the hypothesis that GR-II antagonists would mitigate weight gain and other metabolic effects associated with antipsychotic medications. The group of medications sometimes referred to as atypical antipsychotics, including Zyprexa, Risperdal, Clozaril (clozapine) and Seroquel (quetiapine), are widely used to treat schizophrenia and bipolar disorder. All medications in this group are associated with treatment-emergent weight gain of varying degrees and carry a warning in the label relating to treatment-emergent hyperglycemia and diabetes mellitus.

Other Disorders

We have collaborated with researchers investigating the utility of mifepristone and some of our next-generation selective GR-II antagonists in pre-clinical and human proof-of-concept studies in a wide range of disorders, including alcoholism, post-traumatic stress disorder, Alzheimer s disease, and ovarian cancer.

Research and Development

We incurred approximately $14.1 million, $21.0 million and $18.9 million of research and development expenses in the years ended December 31, 2012, 2011 and 2010, respectively, which accounted for approximately 36%, 65% and 69% of our total operating expenses in these respective fiscal years. For a further discussion, see Part II, Item 7, Management s Discussion and Analysis of Financial Conditions and Results of Operations Results of Operations.

Manufacturing Korlym

As a drug discovery, development and commercialization company, we intend to continue to utilize our financial resources to commercialize Korlym and advance other product candidates rather than diverting resources to establishing our own manufacturing facilities.

We intend to continue to rely on experienced contract manufacturers to produce our product candidates. We have entered into a manufacturing agreement with one contract manufacturer, Produits Chimiques Auxiliaires et de Synthese SA (PCAS), to produce the active pharmaceutical ingredient (API) for Korlym. The FDA approved our commercial use of material produced by PCAS as part of our NDA submission for Korlym. The agreement with PCAS, which was executed in November 2006, was for an initial period of five years with an automatic extension for one additional year and has been extended to June 2013. We are pursuing discussions to continue the relationship thereafter. The agreement calls for us to purchase from PCAS at least 75 percent of our requirements until the expiration of the agreement. If PCAS is unable to manufacture the product for a consecutive six-month period, we have the right to terminate the agreement, without penalty.

We have also entered into an agreement with another contract manufacturer, PharmaForm, L.L.C. (PharmaForm), for the production of Korlym tablets. The agreement with PharmaForm was executed in March 2012 for an initial period of two years. The agreement will be automatically extended for additional one year periods unless one Party gives six months prior written notice that it does not want such an extension. The agreement with PharmaForm may be terminated by either party upon 180 days written notice; we may terminate projects initiated under this agreement with 30 days written notice. There are no minimum purchase amounts under this agreement.

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We are currently in negotiations for a commercial manufacturing agreement with AAI Pharma, our second tablet manufacturer whose facility was approved by the FDA for manufacture of our commercial Korlym tablets in November 2012.

Competition for Korlym

Korlym competes with established treatments, including surgery, radiation, and approved medicines prescribed off-label. Korlym will also compete with Novartis drug, Signifor® (pasireotide) Injection, which the FDA approved in December 2012 for the treatment of adult patients with Cushing s disease (a subset of Cushing s syndrome) who are not candidates for pituitary surgery or for whom surgery did not work. In April 2012, Signifor received marketing approval in the EU. It has Orphan Drug designation in both the United States and the EU. Signifor is a somatostatin analogue that inhibits ACTH production by the pituitary, which leads to reduced cortisol production. In the Phase 3 study that served as the basis for Novartis NDA, the drug normalized cortisol levels in 26 percent of patients. Sixty-seven percent of patients developed hyperglycemia or diabetes. Signifor must be taken twice daily, by injection.

Korlym may also experience competition from compounds under development for Cushing s syndrome. We are aware that Laboratoire HRA Pharma (HRA) has received an Orphan Drug Designation in the United States and Europe for the use of mifepristone to treat a subtype of Cushing s syndrome and has begun a clinical trial in Europe and the United States. If this product is approved for commercialization in the United States and the EU, our potential future revenue could be reduced. We are also aware that Exelgyn Laboratories, which operates as a subsidiary of Medi Challenge (Pty) Ltd., received Orphan Drug Designation for endogenous Cushing s syndrome in Europe, but they have stated that they have not yet conducted any clinical trials.

Many colleges, universities and public and private research organizations are also active in the human health care field. While these entities focus on education, they may develop or acquire proprietary technology that we may require for the development of our product candidates. We may attempt to obtain licenses to this proprietary technology.

Our ability to compete successfully will be based on our ability to develop proprietary products, attract and retain scientific personnel, obtain patent or other protection for our product candidates, obtain required regulatory approvals and manufacture and successfully market Korlym and our future products either alone or through outside parties.

Intellectual Property

Patents and other proprietary rights are important to our business. It is our policy to seek patent protection for our inventions, and to rely upon trade secrets, know-how, continuing technological innovations and licensing opportunities to develop and maintain our competitive position.

Under an agreement with Stanford University, we have licensed exclusive rights to the following issued U.S. patents and any corresponding foreign patents:

U.S. Patent Number	Subject Matter	Expiration Date
6,150,349	Use of GR-II antagonists in the treatment of psychotic major depression	October 5, 2018
6,362,173	Use of GR-II antagonists in the treatment of cocain	