CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 13, 2012
From	Dragos Roman MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA -202107
Applicant	Corcept Therapeutics Inc.
Date of Submission	April 15, 2011; received April 18, 2011.
PDUFA Goal Date	February 17, 2012
Proprietary Name / Established (USAN) names	Korlym /mifepristone
Dosage forms / Strength	Tablet/300 mg
Proposed Indication(s)	Treatment of hypercortisolism in patients with endogenous Cushing's syndrome
Recommended:	Approval

1. Introduction

On April 15, 2011 Corcept Therapeutics submitted a New Drug Application for Korlym (mifepristone) under Section 505(b)(2) of the Federal Food, Drug and Cosmetics Act in support of the following indications: treatment of clinical and metabolic effects of hypercortisolism in patients with endogenous Cushing's syndrome including, specifically, "patients with Cushing's disease who have not adequately responded to or relapsed after surgery", "patients with Cushing's disease who are not candidates for surgery". (b) (4)

. Mifepristone is a glucocorticoid receptor (GR-II) antagonist and the rationale for being used to treat hypercortisolism in Cushing's syndrome is based on its ability to compete with endogenous cortisol at the receptor level, and block the biological activity of cortisol. Korlym is manufactured as a 300 mg tablet and is intended for use once a day orally. Treatment with Korlym is initiated at 300 mg once a day and titrated up to 1200 mg daily based on clinical response and tolerability. Korlym is intended for chronic use. Currently there are no approved drug products for the treatment of Cushing's syndrome; several products are used off label alone or in combination with variable efficacy results.

The mifepristone clinical program for Cushing's syndrome was developed under IND 76,480, which was opened on August 2, 2007 in the Division of Metabolism and Endocrinology (DMEP). (b) (4)

. It should be noted that at the time of opening IND

76,480 for Cushing's syndrome, the Korlym pharmacology/toxicology and clinical pharmacology programs had been quite extensive, and human exposure across a variety of indications and doses exceeded 1100 subjects/patients. The IND was in fact opened with what was planned to be the registration clinical trial (Study C1073-400), the results of which are submitted in the current NDA. This study was planned as a 24-week, open-label, uncontrolled (single-arm), Phase 3 clinical trial to be conducted in 50 patients with Cushing's syndrome and glucose intolerance or diabetes (29 patients in the end) and hypertension (21 patients). Cushing's disease is a rare disease and Corcept has received orphan indication on July 5, 2007 for the "treatment of clinical manifestations of endogenous Cushing's syndrome".   At the time when the IND was opened, DMEP provided answers to a series of questions submitted by the sponsor regarding the development program for the Cushing's syndrome indication. In summary:

- The Division agreed that the toxicology studies conducted up to that time, along with ongoing carcinogenicity studies, would be sufficient for a Cushing's syndrome indication.
- Given the rarity of the disease and the ethical issues raised by conducting a placebo controlled trial in a condition of such severity when there is preliminary evidence of efficacy from published reports, submission of a single Phase 3 clinical study using a single-arm, open-label design was found to be acceptable for an NDA submission.
- The Division provided advice regarding efficacy endpoints selected to be evaluated in the pivotal study, and specifically indicated that, due to the fact that cortisol levels cannot be used as a measure of efficacy in the case of mifepristone, the primary efficacy endpoints should be clinical, i.e. change in blood pressure and/or glycemic control. The Division also advised to use of area under the time vs. concentration curve for glucose during an oral glucose tolerance test as a study endpoint. In the end it was selected as one of the two primary endpoints.
- Following review of the dosing information accumulated in healthy volunteers and across various patient populations studied under mifepristone INDs, the Division recommended that Korlym doses should not exceed a maximum of 20 mg/kg/day.
- The Division also advised that every woman with an intact uterus undergo transvaginal ultrasound at baseline and completion of the study.

In subsequent correspondence (September, 2, 2009) the Division added a request to obtain baseline and end-of-trial endometrial biopsy in order to evaluate the proliferative effect of the drug on the endometrium. In doing so, the Division decided that, given the severity of the condition being studied and the lack of an approved therapy, the potential effects of mifepristone on reproduction should be studied in the registration clinical trial rather than in a dedicated reproductive study that will slow the Korlym clinical program.

In a communication dated March 3, 2010, DMEP asked the sponsor to add baseline and end-of-trial ophthalmological exams to the safety evaluations of the pivotal trial. This request was triggered by the observation of retinal atrophy in the preclinical program in a single animal species (Sprague Dawley rats) that was not confirmed in a second species (i.e. not observed in mouse or dog). As was the case with endometrial biopsies, this request and the subsequent implementation in the clinical trial were made while the trial was in progress.

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It should be mentioned that after the initiation of the pivotal trial the sponsor noticed that the patients enrolled had baseline diastolic blood pressures lower than expected ▓▓▓▓ (b) (4) ▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓ This issue and its implications will be discussed in detail in the efficacy section of this memorandum.

DMEP granted Corcept Therapeutics a pre-NDA meeting that took place on September 14, 2010. Issues discussed at the meeting included Corcept's program for the Cushing's syndrome indication in general, the sponsor's intention to follow a 505(b)(2) regulatory path, the format and content of the NDA, the proposed stability program, and a proposed REMS. With respect to the plan to submit an NDA under Section 505(b)(2) of the FD&C Act, the sponsor expressed their intension to cross reference the nonclinical data from another mifeprestone product (Mifeprex) as the listed drug. They were advised that the nonclinical toxicology studies conducted under IND 76,480 were sufficient to bridge to the nonclinical findings in the already-approved Mifeprex label. During the meeting, the Agency also provided advice to standard CMC, biopharmaceutics, and clinical pharmacology questions. There were no areas of disagreement and DMEP agreed with sponsor's overall plan.

2. Background

Important for establishing an accurate risk/benefit analysis for Korlym in Cushing's syndrome is a clear understanding of the patient population for which Korlym is intended for use, and the complex medical context in which the decision of adding Korlym to the management of patients with Cushing syndrome is made. Cushing's syndrome is a multisystem disorder of cortisol excess. Korlym aims at treating patients with endogenous hypercortisolism (exogenous hypercortisolism, the most frequent cause of Cushing's syndrome, is almost exclusively an iatrogenic condition and is treated by dose reduction or optimization). The hypercortisolism in endogenous Cushing's syndrome (further referred to in this memorandum simply as Cushing's syndrome), results from inappropriate activation of the hypothalamic-pituitary-adrenal (HPA) axis at either the hypothalamus or pituitary level, excess cortisol secretion originating from the adrenal gland (tumors, hyperplasia), or from ectopic sources of corticotropin releasing factor (CRF), adrenocorticotropic hormone (ACTH), or cortisol. By far the most common type of Cushing's syndrome is Cushing's disease, a condition which is due to excessive secretion of ACTH from a pituitary micro- or macroadenoma (it accounts for up to 80% of all cases of Cushion's syndrome).

(Endogenous) Cushing's syndrome is a rare disease. The incidence in the US ranges from 0.7 to 2.4 per 1 million persons per year[1]. With an estimated prevalence of approximately 20,000 patients, Cushing's syndrome meets the regulatory definition of a rare disorder, and, in fact,

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[1] Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. Lancet. 2006 May 13;367 (9522):1605-17.

Korlym has received orphan designation.   A disease of adult age mostly (peak incidence is between 25 and 40 years of age) that affects women more than men (8-fold higher rate of pituitary tumor and 5-fold higher rate of cortisol-secreting adrenal tumors in women with Cushing syndrome than in men), Cushing's syndrome, if left untreated, has an extremely poor prognosis: a mean duration from presentation to death of 4.7 years in Cushing's original series and a mortality rate that is 5-fold higher than that of age and gender-matched subjects[2]. Medical treatment of Cushing's syndrome is secondary to surgical management that can be curative. However, a significant proportion of patients is not cured by surgery. For instance, remission rates following initial surgery for Cushing's disease due to microadenomas of the pituitary are between 70-90% and smaller (50-65%) if due to macroadenomas[3]. Patients who fail surgery have several therapeutic options that include repeat surgery at the original site (pituitary or ectopic) or removal of the adrenals, radiotherapy, or medical therapy. Medical therapy may also be used rarely in some patients who are not candidates for surgery or radiotherapy (including patients with metastatic disease), or when immediate control of the hypercortisolemia is required prior to surgery due to the severity of the disease.

Currently there are no approved medical therapies for Cushing's syndrome. Several drugs that reduce cortisol secretion (adrenal-directed therapy) are used off label in clinical practice (metyrapone, etomidate, ketoconazole) with the goal of reduction or normalization of cortisol secretion. In many respects mifepristone stands alone in the context of the above-mentioned steroidogenesis inhibitors, because it does not reduce cortisol synthesis. Rather, mifepristone reduces the biological effects of the existing endogenous cortisol by competing effectively with it for binding to the type II nuclear glucocorticoid receptors for which mifepristone has an 18-fold higher affinity than cortisol.

The fact that the potential efficacy of mifepristone cannot be measured by quantifying endogenous cortisol secretion (e.g. measuring urinary free cortisol, an important efficacy measure in clinical practice and an equally relevant endpoint in clinical trials) has had direct consequences in the way clinical trials with Korlym have been planned and conducted.   In absence of any other qualified biomarkers of disease improvement, the applicant had to select clinical endpoints. Of the many clinical manifestations of Cushing's disease (glucose intolerance and diabetes, hypertension, obesity, myopathy, bone loss, decreased quality of life, gonadal dysfunction, dermatological changes, compromised immune function, psychiatric symptoms, and fluid and electrolyte disturbances) glucose intolerance and diabetes, on one hand, and hypertension, on the other hand, were selected as primary measures of efficacy for the Korlym phase 3 clinical trial.

Thus, central to this application is whether the Korlym clinical program has provided substantial evidence of effectiveness in adults with Cushing syndrome who have not adequately responded to surgical treatment. This determination is a particularly challenging task for a variety of reasons. First and foremost, Korlym has been studied in a single-arm clinical trial with no comparator; since there are no approved medical therapies for this

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[2] Etxabe J, Vazquez JA 1994 Morbidity and mortality in Cushing's disease: an epidemiological approach. Clin Endocrinol (Oxf) 40:479–484

[3] Blevins LS et al. An approach to the management of patients with residual Cushing's disease. J Neurooncol (2009) 94; 313-319.

indication to compare with, and since the use of a placebo arm in a disease of such severity would be unethical. Such a design in which patients serve as their own control is acceptable because the disease is not expected to show spontaneous improvement, and favorable changes observed at the end of the trial relative to baseline can be presumed to be treatment-related if there are no major confounders. Even so, additional challenges in interpreting the results of the Phase 3 clinical trial are posed by the small size of the study (50 patients), the confounding effects of concomitant medications such as antihypertensive drugs and glucose lowering medications that may interfere with the metrics of the primary efficacy variables, the expected biochemical and clinical variability of the patients enrolled, their relatively diverse surgical, radiological and medical history, and the heterogeneity in Cushing's syndrome etiology (although most patients having pituitary disease, a few had ectopic forms of Cushing's syndrome). Last but not least, methodological shortcomings appear to have been generated in one of the primary analysis cohorts, the "hypertension" cohort, which enrolled patients on the basis of elevated systolic and/or diastolic blood pressure, while diastolic blood pressure only was selected as primary efficacy variable. This memorandum will thus focus on the aforementioned limitations and on the interpretability of the Phase 3 program results with respect to efficacy, in addition to discussing the standard safety findings.

3. CMC/Device

The CMC review (DARRTS 1/12/2012 and 1/17/2012) recommends approval of this application. There are no recommendations for Phase 4 studies. The Office of Compliance has issued on January 12, 2012 an "acceptable" recommendation for the manufacturing facilities.

The active ingredient in Korlym, mifepristone, has a molecular weight of 429.60 g/mol. It is a (b) (4) made to be structurally similar to progesterone and glucocorticoids. Korlym is manufactured as immediate-release tablets and formulated to contain 300 mg of (b) (4) mifepristone (b) (4) sodium starch glycolate NF (b) (4)

hydroxypropylcellulose NF (b) (4) silicified microcrystalline cellulose (b) (4) sodium lauryl sulfate (b) (4) magnesium stearate (b) (4) and (b) (4) film coating (b) (4) . All excipients meet compendial requirements. Mifepristone in Korlym was formulated (b) (4) because of its poor solubility. Korlym will be packaged in two packaging configurations: a 28-count bottle is packaged in a (b) (4) high density polyethylene bottle with a child-resistant closure (b) (4) , and a 280-count bottle packaged in a (b) (4) high density polyethylene bottle with a child-resistant closure (b) (4) .

The CMC review indicates that Corcept has authorization to the relevant DMFs for the drug substance, ingredients, container-closure system, and manufacturing processes. The drug specifications were reviewed and found to be acceptable. Impurities and degradants met ICH

requirements. Based on the stability data submitted, an expiry of 24 months is granted at room temperature.

A categorical exclusion from an Environmental Assessment was granted.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology reviews (DARRTS, 1/20/2012 and 2/7/2011) recommend approval. They do not make any recommendations for additional studies.

The applicant submitted in this NDA a 12-month toxicology study in dogs and a 2-year carcinogenicity study in the mice and rats. Both studies were conducted at the request of the Agency and were in addition to a wide range of preclinical studies previously submitted under IND 76,480. The applicant did not submit any reproductive and developmental toxicology studies of their own; instead they are referencing the nonclinical fertility and genotoxicity data in the Mifeprex® label (Danco Laboratories). Reliance on Danco's data was found to be scientifically valid by the toxicology/pharmacology team on the basis of the demonstration that the active ingredient in Korlym is mifepristone and that the pharmacological/toxicological studies conducted with Korlym demonstrate pharmacodynamic effects consistent with the known effects of mifepristone.

Relevant safety findings of the pharmacology/toxicology program (other then those related to the known pharmacodynamic effect of the drug) include liver toxicity[4], thyroid tumors[5], retinal atrophy, and QT prolongation. The liver and thyroid findings have been attributed to induction of enzyme activity in the liver (mainly CYP3A) that results in hyperplasia and eventually neoplasia, as well as increased thyroid hormone metabolism in the liver. In clinical studies LFT elevation has not been a problem (there were no cases that met the definition of Hy's law, and LFT outlier values were rare, transient, of moderate magnitude, and resolved without intervention or could be explained by underlying liver disease. Thyroid laboratory changes have been minimal (transient TSH elevations with minimal changes in free T4) and are all monitorable (See also Section 8 for clinical discussion). The retinal atrophy (single species observation) and the QTc prolongation observed in dogs will also be discussed in Section 8 of this memorandum.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review (DARRTS 1/13/20012) finds the data submitted in the NDA acceptable. However, due to the fact that mifepristone, the active ingredient in Korlym,

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[4] Elevated liver function tests (LFTs), hepatocellular hypertrophy (especially in rat), hepatocellular toxicity in mouse at doses of about 5X clinical exposure; hepatocellular adenomas (rat-specific).
[5] Thyroid follicular cell adenomas, carcinomas in female rats.

is a CYP 3A4 substrate, and due to the potential pharmacokinetic interaction between mifepristone and ketoconazole (a strong CYP3A4 inhibitor used commonly off label for the medical management of patients with Cushing's syndrome), the clinical pharmacology team recommended a drug-drug interaction study between Korlym and ketoconazole as a post-marketing requirement.

The clinical pharmacology review includes an extensive description of the pharmacokinetics and metabolism of mifepristone, including information collected from Corcept's 18 clinical pharmacology studies[6], as well as information described in other sources such as the Mifeprex label. The pharmacokinetics of mifepristone has been characterized and is relatively well known. Mifepristrone has an absolute bioavailability that varies between 40% and 70% and, due to low solubility, it is believed that absorption at higher doses would be limited. The T_{max} is 1-4 hours and delayed with food for approximately 1 hour after single and multiple doses. The $T_{1/2}$ of mifepristone is 40.7 hours after a single dose and 84.6 hours after multiple dose administration of a clinical average dose 600 mg. Once absorbed, mifepristone is metabolized hepatically by CYP3A4. Six metabolites have been identified, three of them being also active metabolites with peak concentrations reached around 4, 6, and 36 hours, respectively. Both the parental product and its metabolites are protein bound (99% for mifepristone and 96-98% for metabolites). Major binding proteins are α1-acid glycoprotein (which is saturable within the therapeutic dose range) and albumin. Approximately 90% of drug is eliminated in bile and <10% in urine.

The review indicates that the pharmacokinetics of mifepristone is not proportional with dose; following oral administration of a single mifepristone dose of 300 mg to 1800 mg there is an increase in exposure that is not proportional to the increase in dose. Since there is no evidence for facilitated transporter(s) responsible for absorption for mifepristone, which could account for the nonlinear PK, the reviewer proposes that this observation could be explained by the low solubility of mifepristone. Of interest, in the Phase 3 trial, the pre-dose concentrations did not increase significantly as the dose was increased above 600 mg.

Mifepristone is not only a substrate of CYP 3A4 but also an inhibitor. This feature may be responsible for the observation that mifepristone concentrations tends to decrease over time. The clinical relevance of this observation is not clear at this time.

The clinical pharmacology reviewer points out that the effect of strong CYP3A4 inhibitors on the pharmacokinetics of mifepristone has not been evaluated. Ketoconazole is such an inhibitor and is particularly relevant in clinical practice because both ketoconazole and mifepristone are used in the medical treatment of Cushing's syndrome. Although the applicant proposes   (b) (4), understanding the effects that ketoconazole may have on the pharmacokinetics of mifepristone (and labeling appropriately this information) is of particular clinical importance. Therefore I agree fully with the postmarketing recommendation to conduct a drug-drug interaction study with ketoconazole.

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[6] The 18 clinical pharmacology studies include 13 studies in which the pharmacokinetics of mifepristone has been evaluated in different patient populations (healthy subjects, patients with severe renal impairment, moderate hepatic impairment), five *in vitro* studies and a thorough QTc study.

No justification for a body weight cut-off of 60 kg was found despite the use of such a dosing threshold by the applicant in the Phase 3 clinical trials.

Food effect studies conducted with 1200 mg single dose, 1200 mg multiple doses, and 600 mg single dose indicate that food increases Cmax and AUC of mifepristone (e.g. an increase of 19% in Cmax and 29% in AUC following a single dose of 600 mg of mifepristone). Mifepristone is recommended to be taken with food.

Results from a study conducted in patients with severe renal impairment showed no significant change in the pharmacokinetics of mifepristone following administration of 1200 mg of mifepristone.

Finally, based on the known metabolism of mifepristone and the drug-drug interaction studies conducted, the clinical pharmacology reviewer makes the following recommendations:
- No dose adjustment is necessary for patients with hepatic impairment, but doses in excess of 600 mg should not be used in patients with moderate hepatic impairment, and the drug should not be used in patients with severe impairment.
- Concomitant use of Korlym with simvastatin or lovastatin should be contraindicated.
- When given concomitantly with Korlym, substrates of CYP2C8/9 should be used at the smallest recommended doses and closely monitored for adverse effects.
- Other oral drugs with CYP3A mediated metabolism may need the lowest or a reduced dose when used with Korlym.
- Concomitant use of strong inhibitors of CYP3A is contraindicated.
- Mild to moderate inhibitors of CYP3A do not require dose adjustment of Korlym.
- Use of moderate inhibitors of CYP3A4 should be avoided.
- Use of midazolam should be contraindicated.
- Use of CYP2B6 substrates should be avoided.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The main source of clinical data for the Cushing's syndrome indication is Study C1073-400 (further referred to as Study 400), a 24-week, single-arm, multicenter (17 US sites) open-label study conducted in 50 adult patients with Cushing's syndrome. Patients who completed the study and benefited from Korlym were allowed participation in an extension trial, Study C1073-415 (further referred to as Study 415) following a 6-week period of observation off mifepristone. Study 415 is ongoing.

Study 400 enrolled adult patients with a diagnosis of endogenous Cushing's syndrome who had clinical evidence of hypercortisolemia[7], biochemical evidence of cortisol excess[8], and who required medical treatment in the opinion of the investigator. There was no specific metric associated with the clinical determination that a patient was a candidate for medical treatment or not; instead, not unlike a clinical practice scenario, the decision appears to have been based on the best judgment of the caring physician/investigator[9]. Not surprisingly, given the heterogeneity of Cushing's syndrome in general, the etiology of Cushing's syndrome among the patients enrolled in Study 400 was quite diverse, and included Cushing's disease (most patients), ectopic sources of ACTH, or excess of cortisol secretion due to adrenal sources (adrenal carcinoma).

Mifepristone treatment was started in all patients with a dose of 300 mg once a day. This was followed by dose escalations of 300 mg at a time, which were done at several weeks interval in absence of clinical improvement, provided that the drug was well tolerated. The highest allowed doses were 900 mg for patients with weights < 60 kg (this dose could be reached as early as Week 6) and 1200 mg for those with weights > 60 kg (this was achieved as early as Week 10). No patients received doses in excess of 1200 mg (although the protocol allowed exceptions under certain circumstances) and no dose was allowed to exceed 20 mg/kg/day. Dose reductions were also permitted for safety or poor tolerability. If Korlym treatment resulted in oversuppression of cortisol activity and evidence of adrenal insufficiency (an event anticipated based on prior experience with this drug and its known mechanism of action) mifepristone was to be interrupted for ≥ 7 days (given the long half-life of the drug) and treatment with exogenous corticosteroid was to be initiated; if Korlym treatment was re-initiated it had to be done with the initial starting dose of 300 mg.

Two inclusion criteria deserve special attention because they are related in a fundamental way to the clinical endpoints selected for the primary efficacy analysis (glucose control and reduction in diastolic blood pressure). As designed, patients were to be enrolled in Study 400 in two distinct cohorts: a cohort of patients who had either glucose intolerance or type 2 diabetes (from now on referred to, for simplicity, as the "diabetes" cohort because 83% of patients in this cohort had diabetes) and a cohort of patients with hypertension (from now on referred to as the "hypertension" cohort). Please note that there was no randomization to any of these two groups, and patients were assigned to each of them simply according to pre-specified baseline characteristics. Of the 50 patients enrolled, 29 were assigned to the diabetes cohort and 21 to the hypertension cohort. Each cohort had a different prespecified primary

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[7] Patients had to have two or more of the following signs and symptoms: Cushingoid appearance (moon facies, dorsal-cervical fat pad, plethora), increased body weight or central obesity, proximal muscle weakness, low bone mass (DXA T-score < -1.0), psychiatric symptoms (including depression or psychosis), hirsutism and/or violaceous striae and/or acne.

[8] This consisted in above-normal urinary free cortisol (UFC) on at least two complete 24-hour urine collections collected within 4 months of the baseline visit with at least one done during the screening period which was 6 weeks in length (all UFC collections were accompanied by concomitant measuring of urine creatinine to ensure appropriate collection of the urine specimens).

[9] The applicant specifically states that "the study enrolled subjects for whom the investigator had determined that medical treatment of endogenous hypercortisolemia was needed. Medical treatment could have been intended to treat the effects of persistent or recurrent hypercortisolemia after surgery and/or radiation for Cushing's disease, to bridge the period of time for radiation to become effective, when surgery was not feasible, or in subjects with non-pituitary based ACTH-dependent and ACTH-independent disorders" (CSR C1073-400, page 21).

efficacy endpoint and primary efficacy analysis. As such, Study 400 could didactically be seen as two different small trials, one conducted in patients with glucose intolerance or diabetes and the other in patients with hypertension. In these two "trials", the primary efficacy assessments were different but the safety evaluations were identical.

To be enrolled in the diabetes cohort, patients had to show evidence of glucose intolerance[10] or diabetes[11] based on the results of a baseline oral glucose tolerance test or based on standard diabetes diagnostic criteria. Of note, there criteria were not applied to those patients who had previously been diagnosed with diabetes mellitus and were on anti-hyperglycemic medications prior to study initiation (i.e. these patients were allowed enrollment on the basis of prior diagnosis of diabetes). Such patients, however, had to be on stable doses of antidiabetic medications prior to enrollment and no changes in antidiabetic medication(s) were allowed from 2 weeks prior to the initiation of the study drug through its completion[12]. No new antihyperglycemic medications were allowed once enrolled, and patients who required and received additional antihyperglycemic medications during the study were to be discontinued. The primary efficacy analysis for the diabetes cohort was a responder analysis; a responder was defined as a patient who had a $\geq 25\%$ reduction in the serum glucose area under the time vs. concentration curve at end of trial relative to baseline following an oral glucose tolerance (oGTT) test.

The blood pressure criterion required for assignment to the hypertension group included a systolic blood pressure ≥ 140 mmHg <u>and/or</u> a diastolic blood pressure > 90 mmHg; patients were also allowed enrollment if they had a history of hypertension caused by or aggravated by hypercortisolemia and were currently receiving antihypertensive medication(s); such patients had to be on stable doses of antihypertensive medications, and no changes were allowed for 4 weeks prior to enrollment. No new antihypertensive medications were allowed during the trial; if used, patients were to be discontinued[13]. The primary efficacy analysis for the hypertension cohort was also a responder analysis, a responder being a patient that experienced a ≥ 5 mm reduction in diastolic blood pressure. It should be mentioned from the start (and this issue will be further expanded with the actual presentation of the clinical efficacy results) that there is some degree of disconnect between the blood pressure inclusion criterion and the primary efficacy analysis for this cohort in that the above-described inclusion criterion allowed patients to be enrolled with normal diastolic blood pressure, and in fact the mean diastolic blood pressure at baseline (82.9±11.42 mm Hg) was within the normal range.

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[10] Evidence of impaired glucose tolerance was to consist in a plasma glucose level between 140 mg/dL and 199 mg/dL after a 2-hour 75-gram oral glucose load.

[11] Diabetes mellitus had to be confirmed by a fasting plasma glucose ≥ 126 mg on two measurements OR a 2-hour plasma glucose level ≥ 200 mg/dL after a 75-gram oral glucose load.

[12] 19/29 (65.5%) of the patients in the diabetes group fell in this category and used glucose lowering drugs during the trial, including exenatide, sulphonylureas, metformin, DPP-IV inhibitors, or various insulins. Thiazolidinediones were not allowed during the study and for 4 months prior to enrollment.

[13] 10/21 (47.6%) patients used diuretics, 13/21 (61.9%) used drugs that acted on the renin-angiotensin system, 7/21 (33.3%) used beta blocking agents, and 6/21 (28.6%) used calcium channel blockers.

Of note, patients assigned to the diabetes/glucose intolerance cohort were allowed to have concomitant hypertension[14], but patients assigned to the hypertension group could not have diabetes/glucose intolerance. The management of hypertension was different in the diabetes group in that patients were allowed changes in antihypertensive mediations and initiation of new antihypertensive drugs in accordance to standard of care.

The patients' characteristics at enrollment in Study 400 were generally consistent with those of patients with Cushing's syndrome seen routinely in clinical practice. The mean age at baseline was of 45.4 years (range 26 to 71 years). The mean BMI of 35.7 kg/m^2 was consistent with an obese population (range 24.1 to 66.4); mean weight was 99.5 kg (range 61.3 to 198.7 kg), and the mean waist circumference was 119 cm (range 88.5, 178.4); 35/50 (70%) of all patients were female, consistent with the higher prevalence of Cushing's disease in women, and 42/50 (84%) of patients were white. From a pure clinical perspective, 98% of patients had a Cushingoid phenotype, 60% had evidence of hirsutism and skin manifestations such as violaceous striae or acne, 98% had central obesity or were overweight, 54% had proximal muscle weakness, 53% had evidence of psychiatric symptoms (psychosis, depression), and 26% had evidence of low bone mass (T-score < -1.0 by DEXA).

With respect to the underlying diagnosis of Cushing's syndrome, 43 (86%) patients were described as having Cushing's disease, 3(6%) patients had cortisol excess due to adrenal carcinomas, and 4 (8%) patients had an ectopic source of ACTH. For the 43 patients with Cushing disease medical treatment was initiated because of persistence of signs/symptoms of hypercorticolism despite pituitary surgery (i.e. failed pituitary surgery) in 30 (70%) patients, disease recurrence after primary pituitary surgery in 21 (49%) patients, and not being candidates or treatable with surgery in 6 (14%); only one patient had a *de novo* Cushing's disease diagnosis[15]; N.B. patients could have more than one reason for being eligible for medical treatment. Of interest, 18 (42%) patients had received radiation to the pituitary[16]. In retrospect, it would have been desirable to avoid enrolling such patients in an uncontrolled trial because of possible interference with the progression of the disease (improvement of pituitary function following radiation therapy can occur and continue to occur over long periods of time). The significance of this finding will be addressed when the primary analysis results will be discussed.

Several patients received medical therapy in the past, but all patients enrolled were naïve to mifepristone therapy[17]. The applicant indicates that 18 patients were entirely naïve to medical therapy, at least 23 patients received prior medical therapy and 13 of them failed medical

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[14] 79 % patients were also hypertensive in the diabetes group. Mean systolic pressure at screening was 138 mmHg (range 100-181 mmHg) and mean diastolic pressure was 86.4 mm Hg (range 64-116 mm Hg)

[15] Table 14.1.4.1 CSR for Study 400

[16] The duration between the initial radiotherapy and the beginning of the trial was as short as 25, 23 days, several months (7 and 9) but mostly over 1 year and as long as 7 years.

[17] The Division asked the applicant to present more detailed baseline information regarding previous treatments for Cushing's syndrome. In their response the applicant indicated that Study 400 did not enroll patients on the basis of having used or failed prior medical treatments, but rather on the basis of the global assessment of the physician whether medical treatment was indicated, and detailed prior treatment data were available only in 44/50 patients. As such a precise chronology of prior therapeutic interventions (surgical, radiotherapeutic or medical) and for each patient could not be reconstructed and the data presented here is a best estimate.

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therapy with a variety of agents (mostly ketoconazole, only a few used cabergoline, octreotide, and metyrapone or combinations thereof). Patients discontinued prior medical therapi(es) at least 30 days prior to beginning of the trial with some for more than 3 months. All three patients with adrenal cortical carcinoma continued mitotane during the trial (as allowed in the protocol). A carryover effect of previous medications is unlikely because they were discontinued ahead of the trial and many have short half-lives (for instance, ketoconazole, by far the most widely used has a half- life of 2-8 hours.and cortisol elevations follow promptly after being discontinued).

Compliance with Korlym in Study 400 was generally good. It reached 92% in the diabetes cohort for the primary efficacy analysis population, 71.4 % in the hypertension cohort for the primary efficacy analysis population and 100% in completers regardless of cohort. The completion rate was only 68% (34/50) for the whole trial; 69% (20/29) for the diabetes cohort and 67% (14/21) in the hypertensive cohort. It was in anticipation of discontinuations that the applicant prespecified that the primary analyses should be conducted in the mITT population for each cohort.

Finally, due to the fact that Korlym blocks the progesterone receptor as well as the glucocorticoid receptor and may result in pregnancy loss, women enrolled in Study 400 had to have a negative pregnancy test prior to receiving Korlym; in addition, they had to agree to continue using a non-hormonal, medically acceptable method of contraception if they were of childbearing potential. Of note, fertility is significantly decreased in patients with Cushing's syndrome (136 reported pregnancies in the literature[18]).

At the completion of Study 400, patients were allowed to be enrolled in an extension trial following an observation period of 6 weeks off medication. Study 415 was a multicenter, open-label, extension study conducted in patients with endogenous Cushing's syndrome who completed Study 400 and who, in the judgment of the investigator, received clinical benefit from Korlym in Study 400. Of the 34 patients who completed Study 400, 30 patients entered Study 415. Dosing principles in the extension study were identical to those in the pivotal study. The purpose of Study 415 was to collect additional safety data.

Efficacy in the diabetes cohort

The prespecified primary efficacy analysis was a responder analysis of the number of patients who experienced at least a 25% decrease in $AUC_{glucose}$ from baseline to end-of-trial during a 2-hour oral glucose tolerance test. The analysis prespecified that the lower bound of the confidence interval for the proportion of responders should be >20%, a threshold which was chosen as clinically significant on the basis of being very different from the rate of spontaneous remission in the intended population, which is close to zero. The analysis was to

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[18] Lindsay JR, Jonklaas J, Oldfield EH, Nieman LK 2005 Cushing's syndrome during pregnancy: personal experience and review of the literature. The Journal of clinical endocrinology and metabolism 90:3077-3083

be conducted in the modified intent-to-treat (mITT) population which included any study participant who received a total of at least 30 days of Korlym during the 24-week trial[19], and included 25 of the 29 patients in this cohort. The primary analysis indicates that 15/25 (60%) of patients experienced a reduction in $AUC_{glucose}$ and the 1-sided 95% CI lower bound of 42% was greater than the pre-specified threshold of 20% at end-of-trial[20]. The FDA statistical reviewer re-calculated the primary efficacy analysis and agreed with applicant's results. He also computed a 2-sided 95% confidence interval for the response rate. The lower bound of the 2- sided 95% confidence interval was 40.4%, above the prespecified threshold.

Although 40% of patients in the mITT populations did not meet the formal definition of responder, most if them showed a reduction in $AUC_{glucose}$ as illustrated in sponsor's Figure 1 (reproduced below). Specifically, 87% of all patients in the mITT population showed $AUC_{glucose}$ improvements at end-of-trial relative to baseline ranging from 0.8% reduction to 69% reduction[21]. All numerical responses for individual patients are illustrated for the mITT population in Table 17 of the Clinical Review. The table lists only three patients who had worsening in glucose control during the study, and the percent of worsening in AUC glucose in these patients was 4.7%, 26% and 33%.

Figure 1. Cumulative Distribution Function for Percent Change in $AUC_{glucose}$ from Baseline to Week 24/ET: C-DM Cohort (mITT Population)
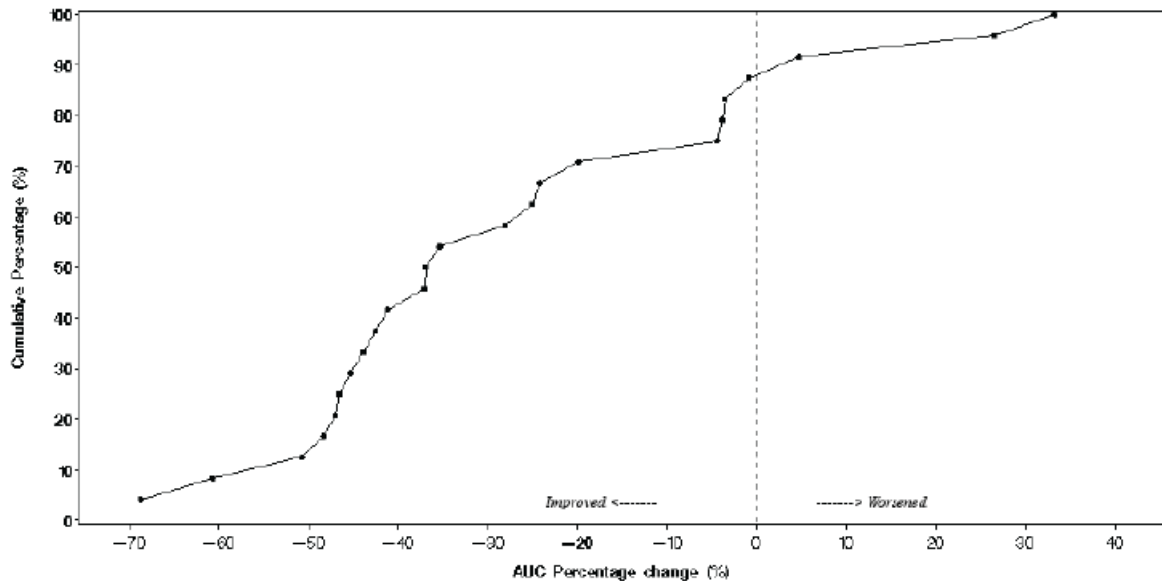
Source: Table 14.2.3.7.

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[19] Additional efficacy analyses were conducted in the Intent-to-Treat population, defined as all patents enrolled who received at least one dose of study medication and the Completer Population defined as all subjects who completed the study through the Week 24 visit and had been at least 80% compliant with the study medication.
[20] The percentage of responders for the ITT and completer populations was 52% and 65%, respectively. The lower bounds for the 1-sided 95% CI for the ITT and completer populations were 35% and 44%, respectively.
[21] 81% showed improvement in the ITT population.

The mean percent reduction in $AUC_{glucose}$ relative to baseline in the mITT population (not shown) was between 22% and 29%[22] (the median was between 19 and 36%[23]); reductions were seen by Week 6 of treatment, the first timepoint for a post-baseline assessment. The statistical reviewer confirmed that the mean change from baseline in $AUC_{glucose}$ was statistically significant (p=.0009).

A timecouse for the individual changes in $AUC_{glucose}$ for each responder is illustrated in Figure 3 of the Clinical Review, reproduced below.

Figure 1.Plot of the Individual AUC values versus Time Profile (Responders in [Diabetes] Cohort of mITT Population)
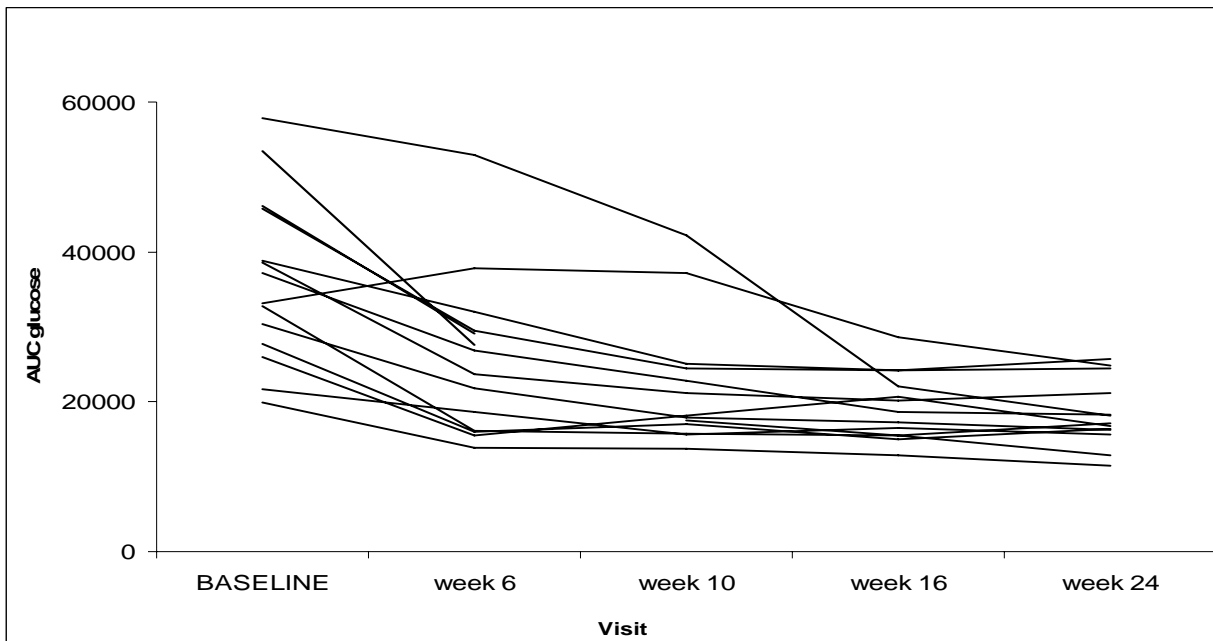
Several secondary and exploratory analyses that related to different aspects of glucose metabolism provided useful additional information that proved to be consistent with the results of the primary efficacy analysis. Of particular significance are the changes in hemoglobin A_{1c} (HbA1c) that occurred during Korlym treatment. As opposed to the oral glucose tolerance test, which remains a relatively specialized test, HbA1c has the advantage of being a widely used measure of glycemic control in clinical practice. Another advantage of measuring HbA1c is that it integrates glycemic exposure over a longer (3 month) period and thus provides a more extended measure of glucose status. Change from baseline to end-of-trial in HbA1c was available for 21 of the 25 patients in the mITT group[24]. The mean change in HbA1c was a reduction of 1.14% (95% CI: -1.70, -0.67) from a baseline value of 7.4 ± 1.5% to 6.3 ± 0.9% at the end of the study (95% CI : -1.70, -0.67). Similar findings were observed for the ITT and completer populations (1.1% and 1.3% HbA1c reductions, respectively)[25]. The FDA statistical

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[22] Week 6: 21.7%; Week 10: 23.5%; Week16: 29.1%; Week 24: 27%.

[23] Week 6: 19.4 %; Week 10: 29 %; Week16: 31 %; Week 24: 36.1%.

[24] 4 subjects did not have a postbaseline HbA1C value.

[25] One more patient did not have HbA1C measurements at baseline, but had elevated HbA1C of 10.3% at screening visit had a reduction to 8.8% at week 24 visit.

reviewer re-calculated the mean change from baseline in HbA1c and arrived at similar values: -1.11 (2-sided 95% CI = (-1.56, -0.65), which were statistically significant (p=.0001) HbA1c was measured in a central laboratory.

Of the 21 subjects in the diabetes group available for HbA1c analyses, 14 had above normal HbA1c levels at baseline, ranging between 6.7% and 10.4%; all of them had reductions in HbA1c by the end of the study (range 0.4 to 4.4%). Table 23 in the Clinical Review (reproduced below) presents baseline and change to end-of-trial in HbA1c for these 14 patients; 8 of them (57 %) normalized HbA1c at the final visit (HbA1c < 6.4%). It is worth noting that only 6 of them received radiation therapy, a potential confounder of treatment. Such a degree of HbA1c reduction occurring over such a relatively short period of time is not expected to be secondary to radiation treatment. Besides, and importantly, all 6 patients had elevated ACTH levels at baseline and the levels remained elevated at Week 24, indicating that the improvement in the glycemic control was not due to a radiation effect on the pituitary.

Table 1. HbA1C and % of AUCglucose Changes from Baseline to Week 24 Visit in Patients with Elevated HbA1C at Baseline in the diabetes cohort (mITT Population)

ID	HbA1C %			oGTT
	Day 1	Week 24	HbA1C Change at Week 24 from baseline	%AUC change at Week 24 from baseline
006003*	8.3	5.5	- 2.8	- 61
008011*	7.4	7.0	- 0.4	- 35
009001	8.0	5.5	- 2.5	- 45
010001	7.8	7.0	- 0.8	- 44
010002	10.4	6.0	- 4.4	- 69
011002*	6.7	5.4	- 1.3	- 37
011003*	7.5	5.8	- 1.7	- 41
017002	8.2	7.2	- 1	-25
018001	7.4	5.9	- 1.5	-51
023001	9.3	6.6	- 2.7	-49
024006*	6.7	5.5	- 1.2	- 43
006001*	8.0	5.9	- 2.1	- 3.5
007004	9.7	8.9	- 0.8	26
024001	6.8	6.7	- 0.1	- 0.8

Normalized HbA1C values in red; table formatting was slightly modified.
Asterisk indicates patients who received radiotherapy.
oGTT= oral glucose tolerance test.

There was no evidence that increases in antihyperglycemic medications could have been responsible for the improvement in glycemic control described above. Not only was there no evidence of dose escalation, but in fact, Korlym treatment was associated with a dose reduction of diabetic medications. Of the 25 patients in the mITT population 19 (75%) were taking at least one antidiabetic medication at baseline (per protocol patients entered on stable antidiabetic regimens and addition of new antidiabetic medication or dose increases of existing

medications were prohibited).   Seven of them (7/19 patients) had a reduction or discontinuation in insulin requirements: 5 had ≥ 50% reduction in median daily dose of insulin and 2 discontinued insulin entirely; one of them also had a reduction in sulfonylurea dose. Per Table 24 of the Clinical Review the median daily dose of insulin decreased from 88 units at baseline to 48 units at endpoint. Other medications remained unchanged (metformin, sitagliptin, exenatide).

Consistent with the previously described observations of improved glycemic control during Korlym treatment, evaluations of other glucose metabolism biomarkers such as Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and insulin levels resulted also in mean reductions (for instance, mean HOMA-IR decreased two-fold).

Finally, glycemic data from Study 400 are consistent with those of case reports published in medical literature and summarized in Section 6.1.10 of the Clinical Review.

Efficacy in the hypertension cohort
As previously alluded to, any attempt to conduct a meaningful analysis of the primary efficacy endpoint for the hypertension group is hampered by methodological shortcomings imposed by the use of a very permissive blood pressure inclusion criterion. As defined in the protocol, the primary efficacy analysis evaluated the percentage of responders in the mITT group, and a responder was defined as any patient who had a reduction of diastolic BP ≥ 5 mmHg at the end of the trial relative to baseline. The enrollment criterion of the hypertension group was a systolic blood pressure ≥ 140 mm Hg <u>and/or</u> a diastolic blood pressure > 90 mm Hg; in addition, patients who had a history of hypertension caused by or aggravated by hypercortisolemia and were treated for it were also allowed enrollment. As such, at screening, of the 21 patients who were enrolled in the hypertensive cohort, 11 had both <u>normal</u> systolic and diastolic blood pressure (all were on antihypertensive medications), 4 patients had normal diastolic and high systolic blood pressure (2 of them were on antihypertensive medications), and only six patients had high diastolic as well as high systolic blood pressures (3 on antihypertensive medications). As a consequence, the mean baseline systolic blood pressure was in the normal range (129 ±16 mm Hg)[26] as was the mean diastolic blood pressure (82.9±11.42 mm Hg)[27].   Under these circumstances, the applicant's intent to measure the antihypertensive effect of Korlym is undermined by the blood pressure findings at baseline, too few patients having actual hypertension to be analyzed for a possible antihypertensive effect of the drug.

Regardless, the applicant proposes a statistical win in the primary efficacy analysis for the hypertensive group with 8 (38%) responders and with a claim that the lower bound of the 1-sided 95% CI of 20.57% was greater than the prespecified threshold of 20%. The FDA statistical review (DARRTS; 1/19/2012) disagrees with the applicant's analysis and points out that the 2-sided 95% confidence interval for the response rate had a lower bound of 16.8% which fell below the 20% margin. In addition, he points out that there were no statistically significant changes from baseline in mean diastolic blood pressure which was -0.1 (2-sided

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[26] Table 26 of the Clinical Review.
[27] Table 21 Clinical Review.

95% CI = (-4.6, 4.6), and p=.980. On the basis of two negative analyses regarding diastolic blood pressure, he concludes that that there is no statistical evidence that Korlym reduces diastolic blood pressure in this cohort.

Several other observations are consistent with the above results. Similar to the observation that there were no changes in mean[28] or median[29] diastolic blood pressures during treatment, there were no mean changes for systolic blood pressure either, as illustrated in Table 26 of the Clinical Review. In addition, applicant's Table 17 ("Cumulative Distribution Function for Change in Diastolic Blood Pressure at Week 24/ET in C-HT Subjects (mITT Population and ITT Population") shows that about similar proportions of patients had reductions or worsening in BP at end of trial.

In the end, I fully agree with both the statistical and clinical reviews that the results of Study 400 fail to demonstrate that Korlym has a blood pressure lowering effect.

Additional efficacy analyses

Several secondary and exploratory analyses are worth mentioning. The mean total body weight decreased by 5.7% at the end of the trial (5.9% in the diabetes group and 5.4% in the hypertension group) and 36/46 subjects (78%) lost weight at the end of the study (20/25 subjects in diabetes cohort and 16/21 subjects in hypertension cohort). This weight loss was associated with a mean reduction in waist circumference of 6.8 cm, a mean reduction in total body fat of 3.6% (5.6 kg), and no mean changes in total lean body mass. There was also an improvement in a key secondary endpoint in which a panel of three experts blinded to the visit sequence and to the patient's Korlym dose adjudicated globally the biochemical and clinical features of Cushing's disease [30]; according to this panel 87% of subjects (40/46 patients) in mITT population were "responders", i.e. had evidence of overall improvement at any postbaseline visit. Although this was a "key" secondary endpoint, due to the subjective nature of the assessment, this analysis should be seen more as exploratory in nature.

Efficacy Conclusions
In final analysis, Study 400 did not provide convincing evidence that Korlym has a beneficial effect on blood pressure. It did not result in statistically significant changes in the responder analysis according to the FDA statistical reviewer, it did not lower the mean systolic and/or diastolic blood pressure, and the percentage of patients who had a reduction in blood pressure was similar to that of patients whose blood pressure actually increased at the end of the trial.

On the other hand, and in clear contrast with the blood pressure results, Korlym had a beneficial effect on glycemic control in a group of 25 patients with either diabetes or glucose

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[28] Baseline: 82.9; Week 6: 82.9; Week 10: 86.1; Week16: 81.6; Week 24: 82.8.

[29] Baseline: 87; Week 6: 86.5; Week 10: 88.5; Week16: 81; Week 24: 81.

[30] Eight categories of assessments: glucose homeostasis, blood pressure, serum lipids, change in weight and body composition, clinical appearance, strength assessment, pychiatric and quality of life assessment, and metabolic bone assessment.

intolerance who had long enough Korlym exposure to allow assessment of a possible metabolic effect on relevant glycemic endpoints (mITT population). Within this cohort the reduction in mean HbA1c was 1.1% and statistically significant. It was achieved with a concomitant reduction is insulin use in several patients, and was associated with a twofold reduction in HOMA-IR (a measure of insulin resistance although this assessment is considered for academic purposes not allowed in labeling), reductions in weight, total body fat and waist circumference. Importantly, the primary efficacy analysis met its prespecified goal. Moreover, taking oGTT as an example, all but three patients had various degrees of glycemic improvements. It should be mentioned that there is no evidence that Korlym is an antidiabetic drug per se. If the development of diabetes and/or glucose intolerance in Cushing's syndrome is solely due to hyperglycemia, blocking the glucocorticoid receptor and counteracting directly these effects of hypercortisolemia is a rational pharmacologic intervention for controlling diabetes in these patients. In the general patient population with diabetes, blocking the glucocorticoid receptor and predisposing the patient to adrenal insufficiency is not a medically sound therapeutic option. Other observed consequences of Korlym therapy such as weight reduction, loss of fat tissue and improvement in global Cushing's syndrome manifestations suggest that benefits may extend beyond glycemic control. However, similar to diabetes management in Cushing's patients, Korlym's effect on these other metabolic parameters are secondary to control of extreme hypercortisolemia circumscribed to well-defined disease states of endogenous overproduction. Efficacy has not been evaluated beyond 6 months of treatment (Study 415 collected mostly safety data).

In final analysis, although Study 400 is an uncontrolled study, there is no evidence that the beneficial glycemic effects observed with Korlym are due to other factors. As previously discussed, spontaneous improvements are not expected in the type of Cushing's syndrome patients enrolled in this trial, nor can the results be attributed to previously received pituitary radiation therapy because only a subset of patients had this type of treatment and, very importantly, ACTH levels remained high during the trial (the expectation would be that, if radiation therapy were to be effective, ACTH secretion would diminish). Another potential confounder for efficacy, antidiabetic medication adjustments, was already analyzed and was not found to be relevant (in fact there was a reduction of antidiabetic medications); finally Study 400 did not enroll patients with cyclic Cushing's syndrome or pseudo-Cushing's syndrome, and the clinical diagnosis and descriptions of the patients enrolled did not match any of these conditions.

8. Safety

All the safety information in this memorandum is derived from Dr. Zemskova's clinical review which summarizes in detail the results of Study 400 and its extension (Study 415), as well as safety data from some 27 studies conducted by Corcept with Korlym in non-Cushing's syndrome patients (mostly healthy volunteers, but also patients with renal and hepatic impairment, major depressive disorder, and Alzheimer disease). This memorandum will focus on safety observations made in the pivotal trial, and will mention the additional sources only when relevant. It will follow a standard description of adverse events in general, and will focus on some adverse events with special significance for labeling. It should be mentioned that, to

a large extent, the adverse event profile of Korlym can be anticipated from its mechanism of action and prior experience with mifepristone use in Cushing's syndrome patients.

The Korlym Phase 3 clinical program for the Cushing's syndrome indication provides safety data obtained from 50 patients treated with Korlym for up to 6 months in the pivotal trial, and 30 patients treated for up to 28 months in the extension trial. Daily Korlym doses ranged between 300 mg and 1200 mg. In Study 400 the mean daily Korlym dose was 643.6 mg; the mean dose was higher in the hypertension cohort (723.9 mg) than in the diabetes cohort (585.4 mg).

8.1 Deaths, serious adverse events, adverse events that lead to treatment discontinuation
There were four deaths in Study 400 and one in the extension Study 415, none of which could be reasonably attributed to Korlym. Of the four patients in Study 400, three had adrenal carcinoma with metastases, and one had ectopic Cushing's disease due to an ACTH-secreting neuroendocrine metastatic carcinoma. All four died due to progression of the underlying malignancy. One patient in Study 415 died due to multiple myeloma and amyloidosis. A basis for a relation between multiple myeloma/amyloidosis, Cushing's disease and/or Korlym therapy cannot be established. There were four additional deaths in other Corcept studies, none related to the study drug[31].

Nonfatal serious adverse events (SAEs) occurred in 13 (26%) patients in Study 400 and in 9 (30%) patients in Study 415. In Study 400 thirteen patients (26%) experienced 23 nonfatal SAEs[32]; seven SAEs were considered by the investigator possibly or probably drug-related; orthostatic hypotension, respiratory failure, confusion, hypokalemia, vomiting, adrenal insufficiency and asthenia (the latter, in the opinion of Dr. Zemskova, could have been also a case of adrenal insufficiency). The SAEs occurred at all dose levels. Three SAEs led to withdrawal from the trial: respiratory failure, cardiomyopathy and asthenia (possibly adrenal insufficiency). In Study 415 a total of 15 SAEs[33] were reported; only one was considered drug-related (hypokalemia).

A total of 34 subjects (68%) completed Study 400. Of the sixteen (32%) subjects withdrawn from the study, half did so because of adverse events (10): cancer progression (2), cardiomyopathy (1), fatigue (1), back and leg pain (1) (same subject), worsening of fatigue (1), respiratory failure (1), gastrointestinal intolerance (1), fatigue (1), increase in pituitary tumor size (1). Three of 30 subjects (10%) discontinued treatment prematurely in Study 415; the AEs that led to the study discontinuation were death due to amyloidosis and development of "multicystic endometrial echo complex".

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[31] Congestive heart failure in a patient with underlying hypertrophic cardiomyopathy, acute polypharmaceutic intoxication, suicide (strangulation), and traffic accident.

[32] Orthostatic hypotension, respiratory failure, confusion, hypokalemia, vomiting, sinusitis, adrenal insufficiency , asthenia (2 events), orthostatic hypotension, foot fracture, intracranial aneurism, erosive gastritis, Legionella pneumonia, chest pain, dyspnea (2) , respiratory failure, migraine exacerbation, pulmonary edema, renal failure , worsening of cardiomyopathy, PE, subcutaneous abscess.

[33] Hypokalemia, pneumonia, hyperglycemia, interstitial lung diseases, melanoma, arthritis, amyloidosis, dyspnea, memory loss, colorectal carcinoma, pulmonary embolism, esophageal carcinoma, worsening of anxiety, pneumonia, subcutaneous abscess.

8.2 Treatment-emergent adverse events

All 50 patients (100%) enrolled in Study 400 experienced at least one treatment-emergent adverse event (TEAE) during Study 400, and 44/50 (88%) experienced TEAEs that were considered related to the study drug. The most common adverse events regardless of attribution (Table 52 of the clinical review) were nausea and fatigue (48%) followed by headache (44%) and decreased blood potassium (34%). Other TEAEs reported by ≥ 10% subjects were arthralgia, vomiting, peripheral edema, dizziness, decreased appetite, endometrial hypertrophy, hypertension, dry mouth, abnormal thyroid function test, back pain, dyspnea, myalgia, sinusitis, diarrhea, pain in extremity, and nasopharyngitis. Although they do not fall in a specific pattern, some of them are consistent with, and expected from, the mechanism of action of Korlym (e.g. endometrial hypertrophy). The Sponsor reported that 88% of subjects (44/50) experienced TEAEs that were considered related to study drug. Drug-related TEAEs that occurred in > 5 subjects were fatigue, nausea, hypokalemia, headache, endometrial hypertrophy, decreased appetite, arthralgia, dry mouth, peripheral edema, myalgia, dizziness, vomiting, and abnormal liver function tests.

Although the majority of TEAEs were considered mild or moderate in intensity, twenty-five patients (50%) experienced severe events. The only severe TEAEs that occurred in more than two patients each were fatigue (4 subjects), nausea and vomiting (3 subjects each). Severe TEAEs that occurred in two subjects each were hypokalemia, dizziness, headache, somnolence, anxiety and respiratory failure.

Twenty subjects (40.0%) experienced at least one TEAE that caused an interruption or reduction in study drug. The most frequent ones were nausea (6 subjects, 12.0%) and fatigue (4 subjects, 8.0%) followed by adrenal insufficiency, vomiting, pain, decreased appetite, headache, anxiety, and dyspnea, which occurred in two subjects each.

Of interest, particularly in the light of the fact that Korlym was anticipated to reduce blood pressure, 12 patients (24%) experienced hypertension, which was considered drug related in about half of them (5 patients). Since hypertension appears to have been associated with hypokalemia in the majority of patients, it is entirely possible that it may due to cortisol's mineralocorticoid effect. The TEAEs of hypertension resolved in 6/12, but it still persisted in the other six patients after the study completion indicating that, at least in these patients, it is likely due to the Cushing's syndrome itself.

The clinical review also notes six TEAEs of the exacerbation of autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, psoriasis, gout, and asthma, with 4 of them considered possibly related to study drug. This observation is compatible with the action of Korlym which, by blocking the glucocorticoid receptor, may prevent the biological action of cortisol and exacerbate such disorders. This observation is relevant and should be communicated in the label.

8.3 Laboratory

There were no clinically relevant changes in mean hematological analytes and no out-of-range values of clinical significance. Similar observations apply to chemistry analytes (electrolytes, BUN, creatinine, bilirubin, glucose, alkaline phosphatase, liver function tests[34]) with the clear exception of hypokalemia. Hypokalemia will be discussed in Section 8.5. The most frequently reported TEAEs related to out-of-range laboratory values were decreased potassium (17/50 patients, 34%) and increased TSH values (9/50 patients, 18%). As expected form the mechanism of action of mifepristone (blocking the glucocorticoid receptor, ACTH and cortisol levels increased during treatment with Korlym)[35].

8.4 Study 415

Similar to observations made in Study 400, all 30 patients followed in the extension study had at least a TEAE; such a high incidence is hardly surprising given that Cushing's syndrome is a condition of high morbidity itself that may be further exacerbated by the underlying cause (tumors oftentimes malignant). Generally, the TEAEs reported in the extension study were similar in type to those reported in the initial Study 400. As such, the adverse event profile observed with extended use of Korlym did not raise additional safety concerns.

8.5 Adverse events of interest

Several adverse events were anticipated prior to the initiation of the Phase 3 program based either on the known mechanism of action of Korlym or on prior experience with Korlym in clinical investigations conducted for a variety of indications. These adverse events were analyzed separately as adverse events of special interest and are briefly summarized next.

8.5.1 Adrenal insufficiency

Since mifepristone blocks the glucocorticoid receptor and cortisol action, its use carries a risk of adrenal insufficiency (AI), as confirmed in Studies 400 and 415 wherein three events of adrenal insufficiency were reported by 2 patients. According to Dr. Zemskova's review 5 other patients had two or more symptoms suspicious of AI: dizziness, fatigue, weakness, hypoglycemia, hypotension, fatigue, lethargy, malaise, nausea, orthostatic hypotension, syncope, and vomiting (the applicant proposed that these patients were having steroid withdrawal). One other patient developed AI in a compassionate use program while receiving concomitant ketoconazole. The events of AI were not associated with any particular dose and certainly not only with the highest dose. It needs to be emphasized that a diagnosis of AI is

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[34] Two patients had ALT elevations > 2 X ULN. Patient # 09-001(Cushing's disease) had transient LFT elevation of 2.6 and 2.9 X ULN at Week 6 and 10 visits, and 3.6 X UNL at the Week 8 visit; AST was elevated 2X ULN at the Week 8 visit. ALT and AST normalized at Week 16 visit and remained normal thereafter. This patient had a medical history of fatty liver prior to the study enrollment. She also had an isolated ALT elevation of 4.8 X ULN during Study 415 and normalized at the next visit off medication, which turned out to be the last study visit. Patient # 17-002 (Cushing's disease) had a single elevation of ALT of of 2.1 X UNL at Day 14) visit, that normalized thereafter. There were no concomitant bilirubin elevations,

[35] Baseline mean ACTH 66.1 (range 0-345) ng/L. Mean ACTH values more than doubled on treatment (around 130-140 ng/). The increase was seen by Week 10. Serum cortisol increased from baseline to week 10 and stabilized thereafter (658.1 nmol/L ± 274.8 nmol/L at baseline, 1082.3 nmol/L ± 522.3 nmol/L at week 10 and 984.2 nmol/L at week 24, respectively). Levels of urinary free cortisol varied throughout the study: the levels were the highest at Week 10 visit as compared to baseline values (1008.9 nmol/24 hr ± 2895.0 nmol/24 hr and 2835.78 nmol/24hr, respectively), than slightly decreased at Week 16 visit, but increased again at Week 24 visit (1938. 9 ± 3613. 3 nmol/24 hr).

very challenging for patients with Cushing's syndrome on Korlym because the practitioner can not rely on traditional biochemical markers (cortisol levels remain elevated during treatment with Korlym) and the diagnosis has to be made entirely on clinical symptoms which are non-specific. The risk of adrenal insufficiency should be added to the warnings and precautions section to increase awareness for the practicing physician, raise the level of suspicion for diagnosis and corrective intervention (Korlym discontinuation and glucocorticoid supplementation, and resumption of Korlym at a lower dose). Consideration should be given to a Boxed Warning intended to highlight the difficulty of making a diagnosis of AI and the increased vigilance needed for such diagnosis.

8.5.2 Endometrial proliferative effect

Mifepristone is a known antagonist of the progesterone receptor and, as such, it promotes unopposed endometrial proliferation that may result in endometrium thickening, cystic dilatation of endometrial glands, and vaginal bleeding. In a patient population consisting of 35 females (26 premenopausal and 9 postmenopausal) evaluated in Study 400, the thickness of the endometrium more than doubled during Korlym treatment. In premenopausal women it increased from a mean of 6.14 mm at baseline to 15.7 mm at end-of-trial; in postmenopausal women the increase was from 2.75 mm to 7.35 mm. Although there was a small decline at the 6-week follow-up visit, the endometrial thickness remained above mean baseline values: 14.1 mm and 5.5 mm in pre- and postmenopausal women, respectively. Data on possible recovery beyond 6 weeks are not available.

Increase in endometrial thickness was reported as a TEAE in 10 of 35 females (29%). Vaginal bleeding occurred in 5/35 patients (14%). When available[36], endometrial biopsies showed benign endometrial hypertrophy (two cases of atypical changes were described, one that was present before treatment initiation and one that was not confirmed on final pathology report). Of interest, vaginal bleeding resulted in gynecological procedures in four patients; three of them ultimately elected to have hysterectomies in order to continue Korlym treatment.

In the extension study 3/20 (15%) women had endometrial thickening and all three had vaginal bleeding as well. Two patients experienced vaginal bleeding without endometrial thickness. Thus, 25% of patients experienced vaginal bleeding in this extension study. As in the pivotal study, no relationship to a specific dose and no time-dependency could be established.

Endometrial changes and vaginal bleeding are not surprising observations given the known antiprogesteronic effect of Korlym and the unopposed estrogenic proliferation that it promotes. These findings should be clearly articulated in the Warnings and Precautions of the Korlym label. Patients at risk should be considered for Korlym treatment only cautiously if they have conditions that may predispose to bleeding or endometrial proliferation, and the label should contain information that effects of treatment over 12 months have not been investigated, and that the risk does not appear to be related to a specific dose.

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[36] 7 out of 35 patients had biopsies, all done postbaseline. No baseline biopsies were available due to the late implementation of the protocol amendment that mandated baseline and end-of-trial biopsies.

8.5.3 Hypokalemia

Although Korlym has high affinity for the glucocorticoid receptors (GR-II) it can also bind to the mineralocorticoid receptor (GR-I), albeit with low affinity. In addition, blocking of GR-II at pituitary level results in an increase in circulating ACTH and cortisol levels and increased mineralocorticoid effect since cortisol itself had such activity, albeit weak. Regardless of which of the above mechanisms may occur or may be dominant *in vivo*, there is a theoretical risk of mineralocorticoid receptor activation, with subsequent hypokalemia, edema, hypertension and metabolic alkalosis. This risk was indeed confirmed in both Study 400 and Study 415, wherein hypokalemia (defined as a potassium level ≤ 3.4 mEq/l) was a common TEAE. In Study 400, Korlym treatment was associated with laboratory evidence of hypokalemia in 22/50 patients (44%) and 17 of these 22 observations of hypokalemia were also considered severe enough to be reported as TEAEs. One event of hypokalemia was reported as an SAE and four patients had severe hypokalemia (serum K ≤2.5 mEq/L). Same patients had ≥ 1 event of hypokalemia during the study. . Dr. Zemskova notes that events of severe hypokalemia were preceded by declining potassium levels of lower magnitude which suggests that monitoring potassium levels may lead to early diagnosis and timely corrective intervention. No clear association of the time of development of hypokalemia relative to Korlym treatment duration and no association with any specific dose could be observed (the dose of Korlym ranged between 300 to 1200 mg at time of the event). Serum potassium levels in all patients are summarized clearly in Table 45 of the Clinical Review for Study 400 and in Table 46 for Study 415. Hypokalemia observations in Study 415 were consistent with those made in Study 400.

Thus, hypokalemia should be listed prominently as an adverse occurrence in Section 5 of the Korlym label (Warnings and Precautions) along with the need of periodic monitoring of serum potassium, the reversibility with treatment (all events of hypokaliema resolved with oral or IV potassium supplementation), the potential risk of concomitant use of diuretics (11 patients were receiving diuretics at time of the event), and the fact that some events were associated with signs of apparent mineralocorticoid excess such as edema, alkalosis, and/or hypertension.

8.5.4 Increased TSH levels

In Study 400 the mean TSH levels more than tripled (1.2 mU/l at baseline and 4.2 mU/l at week 24) and returned to baseline within 6-weeks following treatment discontinuation, while the mean free T4 levels changed only minimally during the trial[37]. Eight patients developed elevated out of range TSH values at end of the trial (Table 47 of the Clinical Review) but they all returned to normal at the 6-week follow-up visit, off Korlym. Interestingly, for 3 of them there was a decline in free T4 levels below the lower range of normal, but all 3 normalized at follow-up. One patient was started on levothyroxine at baseline and one at end of trial (the decision was investigator's decision and not protocol-specified; the TSH elevation was mild and there were no changes in T4). Similar results were observed in the extension study (a mild increase in mean TSH, a normal mean free T4, and occasional elevations of TSH without changes in free T4). The above-described changes in thyrotropin levels that were observed during Korlym treatment appear to be transient and reversible and not always associated with

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[37] 14.4 pmol/L at baseline, 12.4 pmol/L at the end of the trial and 13.7 pmol/L at follow-up.

free T4 changes. The clinical significance of these changes is not clear but they should be described in the label.

8.5.5 Ophthalmological evaluations

Ophthalmological exams were performed on 20 of 30 patients enrolled in the Study 415 (by the time the request for ophthalmological evaluations was issued and implemented, Study 400 was already completed). No evidence of retinal atrophy was identified in any of these patients. Exposure to Korlym during the Phase 3 program extended from a minimum of 12 moths (20 patients), to 18 months (12 patients), and to 24 months (5 patients).

8.5.6 Evaluation of changes in the size of the pituitary tumor

A potential effect of Korlym treatment on the size of pituitary tumor in patients with Cushing's disease was evaluated by comparing pituitary MRIs obtained at various times during Korlym treatment to baseline measurements. Paired MRIs were available for 35 patients and were read centrally. Only 16/35 patients had visible pituitary tumors at baseline. The size of tumor increased in 3 patients, marginally in two, and in the third one the tumor turned out to have been malignant. For one additional patient there was some question whether the tumor regressed at one timepoint only to grow back to a similar size at a subsequent measurement, but these changes could very well have been the results of methodological errors. For the remainder of the patients there was no increase in tumor size. Therefore, based on this limited sample of patients, there is no distinct evidence that Korlym may influence tumor size one way or another.

8.5.7 QT interval prolongation

Corcept's clinical pharmacology program identified a concentration-related inhibition of hERG channel by mifepristone and its three major active metabolites, as well as a slight QTc prolongation (6-8 msec) postdose in a chronic dog study conducted at clinically relevant exposure (~1X the MRHD of 1200 mg/kg). The applicant has evaluated a potential QT prolongation effect of Korlym in a thorough QT study conducted in healthy subjects (Study C1073-300)[38]. This study, was formally reviewed by the Interdisciplinary Review Team (IRT)) (DARRTS, 10/21/2011) and found to be inconclusive because the assay sensitivity was not established and small changes in QTc interval could not be excluded. The consult concludes that at the therapeutic (600 mg) and supratherapeutic (1800mg) Korlym dose "there is no detectable relationship between mifeprisone exposure and the ΔΔQTcI-interval [placebo corrected change from baseline in individually corrected QT interval]. However, a dose-dependent increase observed in the response at steady-state was observed. It is likely that the response has reached a plateau and ΔΔQTcI-interval prolongation is not anticipated at higher exposures". The ECG data in the clinical trial was not reviewed by the IRT team. It is summarized descriptively by Dr. Zemskova in the clinical review (Section 7.3.5.2 and 7.71), but the data are not controlled and this limits strong inferences. QTc prolongations were

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[38] This was a randomized, blinded, parallel design 14 day study, conducted in 180 healthy male subjects who were randomized to mifepristone 600 mg, mifepristone 1800 mg, placebo, and a single oral dose of moxifloxacin 400 mg.

observed in several patients. There were no adverse events of torsades or sudden death but a trial of only 50 patients is not expected to detect this rare event. In the absence of a conclusive study to negate a QT prolongation effect of mifepristone in humans, and given the existing signal in the preclinical studies, it seems prudent to indicate a potential risk of QT prolongation in the Warnings and Precautions Section of the Korlym physician labeling.

8.5.8 HDL-cholesterol reductions

Reductions in HDL-cholesterol were assessed in a dedicated 14-week, placebo-controlled study that investigated the effect of 600 mg of Korlym study (Study C1073-425) which showed that Korlym produced a significant decrease in HDL levels compared to placebo, and had little effect on LDL, triglycerides, VLDL-C and ApoB. This finding was consistent with the findings observed in Study 400 wherein HDL-cholesterol decreased from 1.6 (0.7) mmol/L at baseline to 1.1 (0.3) mmol/L at end-of-trial; the mean baseline subtracted change of 0.37 mmol/L represents a 33% reduction (the median reduction was 20 %).   The clinical significance remains unknown but an unfavorable cardiovascular effect associated with long-term use cannot be excluded.

8.5.9 Rash

Mifepristone use has been associated with the development of a general macular-papular eruption that could involve the trunk, extend to the extremities and face, is frequently associated with pruritus but only rarely with systemic symptoms. All events of rash were reported to have been treated with topical agents, antihistamines and/or glucocorticoids and resolved after discontinuation of mifepristone. No evidence of Stevens-Johnson syndrome or Toxic Epidermal Necrolysis has been reported in any of the trials. The highest, incidence of rash was observed in a study conducted in healthy volunteers. Interestingly the rash did not recur on re-challenge.

Safety conclusions

Despite the limitations imposed by a relatively small clinical trial and by the absence of a control group, there is a distinct pattern of adverse events that is emerging from the Korlym clinical program, which should constitute the basis for safety labeling. To a large extent, these safety observations, be it serious adverse events, treatment-emergent adverse events, adverse events resulting in patients discontinuing Korlym treatment, or relevant laboratory observations, are mechanistically anticipated pharmacodynamic effects, largely predictable and monitorable. They include adrenal insufficiency and associated manifestations, hypokalemia, and endometrial proliferation/vaginal bleeding. Some potential safety signals that were observed in the preclinical studies (i.e. QT prolongation), have a weak signal in the human program but cannot be formally ruled out and therefore should be labeled accordingly; the same can be said about thyrotropin elevation, which has been seen in animals but only mildly in the clinical program. Several adverse occurrences that have been seen consistently and cannot be explained on the basis of mifepristone's mechanism of action are skin rashes and HDL-cholesterol reductions. Finally, retinal atrophy and expansion of pituitary tumor size have not been evaluated in every single patient, but the evidence accumulated to date does not indicate a safety signal. In summary, the safety profile of Korlym is acceptable in view of the potential benefit for a disease with limited medical options , the adverse events that Korlym

may trigger can be identified, and it appears that they can be monitored and managed by health care providers familiar with the clinical and biochemical manifestations of Cushing's syndrome.

Dose selection

The Korlym clinical program has established a starting dose (300 mg once daily), a titration regimen, and a range of doses (300 mg to 1200 mg one daily) that provides evidence of efficacy and is reasonable safe. For Study 400 the average dose was 585 mg in the diabetes cohort and 723 in hypertension cohort. Most patients received doses in the 300 to 900 mg per day range, but patients were frequently titrated during the trial and only a minority of patients received a stable dose regimen. At the end of the trial, most responders in the diabetes cohort were on 600 mg of Korlym (47%) and 1200 mg (33%). The clinical pharmacology review indicates that higher doses were not necessarily associated with higher drug exposure. Whether this was a consequence of the poor solubility of Korlym or has another explanation, is not entirely clear.

In Study 415, 80% of patients received stable doses of Korlym (27% received 600 mg and 33% received 1200 mg), suggesting that once a dose affiliated with a clinical response is established it tends to remain stable over the length of time studied.

The clinical pharmacology review does not find pharmacokinetic evidence to support different dosing for patients < 60 kg or > 60kg. This distinction, present in the Study 400 protocol, should be abandoned in the Korlym label.

Finally, it should be mentioned that decisions regarding dose titration in Study 400 benefited from having oral glucose tolerance tests performed regularly, which is not done routinely during the management of patients with type 2 diabetes. Therefore, for labeling purposes, the glycemic goals may need to be defined a little more broadly and include HbA1c and standard glucose measurements.

9. Advisory Committee Meeting

There was no Advisory Committee Meeting held for this application.

10.   Pediatrics

Korlym has received orphan designation on 7/05/07 for the "treatment of clinical manifestations of endogenous Cushing's syndrome". Therefore, the requirements of the Pediatric Research Equity Act do not apply to this application.

11. Other Relevant Regulatory Issues

Division of Scientific Investigation

Two clinical sites that participated in the pivotal study (Study 400) were inspected. The sites were selected on basis of the number of patients enrolled (8 patients each). In one site no deficiencies were identified. In another site isolated violations were observed (one patient in the diabetes cohort and two patients in the hypertension cohort had prohibited medications initiated or increased, two patients were enrolled in the hypertension arm with values above the predefined exclusionary thresholds, and blood pressure measurements did not follow strictly the protocol instructions). These violations were reported in the actual datasets submitted with the NDA and were taken into consideration during the review. The DSI consult observes that the primary endpoint data were verified at both sites and that there was no evidence of underreporting of adverse events. In final analysis the above-reported deviations/violations of the protocol were not judged to be of significance and did not impact the conduct of the study and the validity of the data.

Financial disclosures and compliance with Good Clinical Practice standards

Dr. Zemskova's review indicates that the applicant has submitted FDA Form 3455 and that all investigators were certified to have no conflict of interest. She also confirms that all studies were conducted in accordance with the principles of Good Clinical Practice, were consistent with applicable local regulations and with ethical principles laid down in the Declaration of Helsinki, that patients had to sign informed consent prior to receiving study drug, and the study protocols had to be approved by Institutional Review Boards.

Proprietary Name

A Division of Medication Error Prevention and Analysis (DMEPA) consult has reviewed the proprietary name Korlym and found it to be acceptable from both a promotional and safety perspective (this is the 3rd proposed proprietary name; two other names, Corlux and ⬛⬛⬛ (b) (4), have been have been found unacceptable due to vulnerability to name confusion).

Interdisciplinary Review Team consult

A consultation was provided by the Interdisciplinary Review Team regarding a thorough QT study. This consult was discusses in Section 8.5.7 of this memorandum.

DRUP Consult

DMEP requested a formal consult from the Division of Reproductive and Urologic Products (DRUP) regarding the integrity of the reproduction function in females with Cushing's syndrome. The purpose of the consultation was to assess reproductive risks of Korlym, which contains the same active ingredient (mifepristone) as Mifeprex, which is approved for medical termination of pregnancy up to 49 days post conception. In summary, the consult states that:

- although pregnancy is possible in patients with Cushing's disease who are treated with daily doses of mifepristone ≥300 mg, it is likely to occur at a significantly reduced rate (low dose mifepristone prevents ovulation in 13-20% of non Cushing syndrome women and may also disrupt normal endometrial maturation preventing implantation of a fertilized egg)
- that chronic use of mifepristone in non-Cushing women has an intrinsic risk of pregnancy termination albeit lower than when used in combination with a prostaglandin; the risk is 64-85% for mifepristone alone and over 90% when used with misoprostol
- nonhormonal contraception is necessary in order to prevent pregnancy and subsequent pregnancy loss during Korlym use.

Risk Evaluation and Mitigation Strategy (REMS)

In response to applicant's proposed Risk Evaluation and Mitigation Strategy which consisted in REMS with Medication Guide and ETASU, the Division has consulted extensively with the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology, the Maternal Health Team, and the Office of Review Policy. The Division's recommendation was that a REMS with ETASU was not warranted for Korlym use in patients with Cushing's syndrome. This recommendation was made in acknowledgment of the fact that Cushing's syndrome is a rare disease that is managed by physicians trained in understanding the complexity of this condition, who oftentimes provide care as part of a multidisciplinary team in referral centers. The recommendation was presented and discussed at a REMS Oversight Board meeting, and was also the subject of a Center Director's briefing, The Division received concurrence that a REMS with ETASU was not necessary for the Cushing's syndrome indication. In final analysis it was agreed that the main risks associated with Korlym use in patients with Cushing's Syndrome (adrenal insufficiency, hypokalemia, endometrial thickening and vaginal bleeding, unintended fetal loss, and risks due to drug-drug interactions) could be communicated effectively to physicians via information contained in the package insert, while a non-REMS Medication Guide could achieve the same function for individual patients. Specifically, the Medication Guide could inform patients not only about the risks of adrenal insufficiency, hypokalemia, vaginal bleeding, QT prolongation, and medications they need to avoid, but also about the need to have a negative pregnancy test prior to Korlym treatment initiation and following any discontinuations longer then seven days, about the need to use a medically effective form of contraception during Korlym treatment to reduce the albeit low risk of pregnancy and of unintended Korlym-induced pregnancy termination. Patients who do not want to face this extremely small but nevertheless real risk have the option to forego medical treatment with Korlym.

12.   Labeling

The physician labeling and the non-REMS Medication Guide are almost finalized at this time. I am in agreement with the recommendations made by the participating disciplines. Of note, the label contains a Boxed Warning alerting physicians about the risk of pregnancy loss (and the need to exclude pregnancy prior to initiating treatment with Korlym), and two limitations of use: one indicating that Korlym should not be used in the treatment of type 2 diabetes unless it is secondary to hypercortisolemia; another indicating that CYP3A inhibitors should be used only when necessary and, if so, the lowest Korlym dose should be used.

13.   Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I am in agreement with the approval recommendations made by all contributing disciplines and with the primary clinical review recommendation that Korlym should not be approved for <u>any</u> patients with Cushing's syndrome, but only for those who have glycemic complications due to Cushing's syndrome, i.e. glucose intolerance or type 2 diabetes.

- Risk Benefit Assessment

The potential benefit of Korlym in the management of hyperglycemia secondary to hypercortisolemia in patients with Cushing's syndrome outweighs the risks associated with Korlym treatment. The risks identified to date are monitorable and largely preventable in the hands of a health care provider with expertise in the management of this disease.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

It is important to recognize that patients with Cushing's syndrome, due to the rarity and complexity of the disease, are managed mainly by endocrinologists, and oftentimes by a multidisciplinary team in large medical centers or specialty clinics. The existing risks associated with Korlym therapy could be communicated effectively to these physicians via information contained in the package insert. A non-REMS Medication Guide could achieve the same function for individual patients. As such, the Medication Guide could inform patients not only about the risks of adrenal insufficiency, hypokalemia, vaginal bleeding, QT prolongation, but also about the need to have a negative pregnancy test prior to Korlym treatment initiation and following any discontinuations longer then seven days, about the need to use a medically effective form of contraception during Korlym treatment to reduce the albeit low risk of pregnancy and of unwanted Korlym-induced pregnancy

termination. Patients who do not want to face this extremely low but nevertheless real risk have the option to forego medical treatment with Korlym.

- Recommendation for other Postmarketing Requirements and Commitments

I am in agreement with the two postmarketing studies (both PMRs) proposed by the clinical reviewer and the clinical pharmacology reviewer. They are:
1) A postmarketing drug utilization study aimed at better characterizing the incidence rates of endometrial hyperplasia, retinopathy, and major adverse cardiovascular events. Evaluations of endometrial hyperplasia and retinopathy have been implemented only after the pivotal study was initiated and thus precise knowledge of the frequency of these adverse events is not entirely understood. In addition, the risk, if any, of the HDL-lowering effect due to Korlym remains to be characterized. This study will provide a denominator for the above-mentioned adverse events and will provide information on dosing, duration of use of the product, age, gender, and indication for treatment.
2) A drug-drug interaction clinical trial whose goal is to quantify the change in mifepristone exposure following co-administration with ketoconazole. Since the degree of change in exposure of mifepristone when co-administered with strong CYP3A inhibitors is unknown, and since ketoconazole is a strong CYP3A4 inhibitor, the concomitant use of these medications may present a safety risk, and needs to be properly assessed and labeled.

- Recommended Comments to Applicant

The requirement for the two postmarketing studies listed above should be added to the Action Letter.