CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Division / Office	DMEP
Reviewer Name(s)	Zemskova Marina, MD
Review Completion Date	January 13, 2012
Established Name	Mifepristone
(Proposed) Trade Name	Korlym
Therapeutic Class	
Applicant	Corcept Therapeutics
Formulation(s)	Oral tablets
Dosing Regimen	300-1200 mg once a day
Indication(s)	Endogenous Cushing's syndrome
Intended Population(s)	Adults

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1 Recommendations/Risk Benefit Assessment

Mifepristone (Korlym) is a glucocorticoid receptor antagonist that is proposed by Corcept Therapeutics for the treatment of clinical and metabolic effects of hypercortisolemia in patients with endogenous Cushing's syndrome. Mifepristone is currently marketed in the US by another company under the brand name Mifeprex™ for the indication of early termination of pregnancy. Corcept submitted this NDA (20705) to the Division under Section 505(b)(2) on April, 2011 . The proposed starting dose for Korlym is 300 mg; the dose may be escalated further in 300-mg increments to a maximum of 1200 mg once daily based on the assessment of clinical response and tolerability.

Currently there is no approved medical therapy to reduce the effects of hypercortisolemia in patients with Cushing's syndrome in the US.

1.1 Recommendation on Regulatory Action

According to my review of clinical data, I recommend approval of the use of Korlym 300 -1200 mg in patients with Cushing's syndrome and glucose intolerance or diabetes induced by hypercortisolemia.

A daily administration of Korlym was not effective in producing a clinically meaningful improvement of hypertension induced by hypercortisolemia in patients with Cushing's syndrome. Therefore, Korlym should not be recommended for the treatment of hypertension in patients with Cushing's syndrome.

1.2 Risk Benefit Assessment

Korlym (Mifepristone) is a potent and specific antagonist of the type II nuclear glucocorticoid receptor (GR-II) and competes with cortisol for the binding to the receptor, preventing the biological effect of cortisol. Importantly, it does not decrease cortisol level. Given that the Sponsor has demonstrated the drug product's efficacy and acceptable safety in patients with Cushing's syndrome, Korlym can play a useful role in this population.

Efficacy

The Sponsor conducted a single Phase 3 pivotal study, Study C1073-400 (referred to as "Study 400" in this review), in support of the proposed indication. The study was an open label study conducted in subjects with clinically significant hypercortisolemia who had not responded adequately to surgical or radiation treatment for Cushing's disease, and in subjects with the other forms of ACTH-dependent and ACTH-independent endogenous Cushing's syndrome. An open label design was chosen because of the lack of an approved comparator drug. Fifty patients were enrolled in the study and received treatment with Korlym for 6 months. The initial dose of Korlym was 300 mg orally once a day that was titrated up to 1200 mg once a day based on efficacy and safety every 4 weeks or more frequently, if necessary. Patients' enrollment in the

study was based on the presence of two major complications associated with hypercortisolemia: impaired glucose tolerance/diabetes mellitus (the so called "C-DM cohort") or hypertension (the "C-HT cohort"). There was no randomization to the any of these 2 cohorts; patients were assigned based on baseline characteristics The study demonstrated that administration of Korlym to the 25 subjects in C-DM cohort resulted in a significant improvement in glycemic abnormalities: 87% of patients demonstrated an improvement in glycemic control as assessed by the percent decrease in the area under the two-hour blood glucose response curve ($AUC_{glucose}$) at the end of the study, and 60% (15/25 subjects) of patients had a reduction in $AUC_{glucose}$ of more than 25% (co-primary efficacy endpoint). Because the lower bound of the 1-sided 95% confidence interval (CI) was greater than 20% (42%), this response rate of 60% was statistically significant. When standard 2-sided 95% CI was applied, the lower CI was 40.4%, still statistically significant. The mean change from baseline in $AUC_{glucose}$ was -8722 mg/dL*2hrs (2-sided 95% CI = (-13184, -4260), p=0.0009) from a baseline mean of 30670 mg/dL*2hrs. The improvement in glycemic control occurred early during the study - at Week 6 visit. Although the $AUC_{glucose}$ is not a standard endpoint in the assessment of the glucose control and may be affected by the other factors such as diet, exercise, and stress, the improvement in this primary efficacy parameter was supported by a significant reduction of HbA_{1C} levels, a secondary efficacy endpoint. HbA_{1C} provides a more reliable and validated measure of long-term glycemic control. There was a clear improvement in HbA_{1C} by the end of the study: mean values decreased by 1.1% (2-sided 95% CI = (-1.56, -0.65), p=0.0001). Of the 12 subjects in the C-DM cohort with baseline HbA_{1C} values > 7% (mean 8.5%), nine had reductions in HbA_{1C} values to less than 7% at the end of the study. Of these, six subjects had HbA_{1C} values within the normal range (< 6%) at the end of the study. Moreover, seven of 19 subjects who were treated with antidiabetic medications at baseline had a reduction in the number and/or doses of antidiabetic medications by the end of the study; five of 12 subjects who were on insulin therapy had a dose reduction of 50% or more by the end of the study. The majority of patients with impaired glucose tolerance or diabetes responded to the doses < 600 mg (9 of 15 patients).

Other efficacy findings were supportive of the primary findings of the efficacy of Korlym in the cohort of patients with impaired glucose tolerance or diabetes induced by hypercortisolemia. Decrease in insulin levels and increase in insulin sensitivity (as evaluated by the homeostatic model assessment of insulin resistance (HOMA-IR)), decrease in body weight and waist circumference, and improvement in body composition with decrease in total and abdominal fat content was consistent with the improvement in glycemic control.

The study met the other primary endpoint and demonstrated that 38% (8/21 subjects) of the subjects in C-HT cohort had an improvement in diastolic blood pressure (DBP) by 5 mm Hg or more. This result was statistically significant because the lower bound of the one-sided 95% CI was greater than 20%, the pre-specified margin of clinical significance. The clinical significance of the improvement in blood pressure control in these patients has to be called into question because of the following:

- Hypertension was defined at baseline as systolic blood pressure (SBP) ≥ 140 mmHg and**/or** diastolic blood pressure > 90 mmHg. Thus patients with normal DBP (but elevated SBP)

were eligible for the study. Further decrease of normal DBP is of unknown clinical significance.

- The median DBP values in all C-HT cohort patients were normal at baseline and decreased at the end of the study by 6 mm Hg (from 87 mmHg to 81 mmHg, respectively). The mean DBP values did not change at the end of the study as compared to baseline values.
- The overall improvement in DBP was less striking than improvement in glycemic control: only 50% of patients in C-HT had some improvement in DBP. Moreover, the other 50% of patients had worsening of DBP control (in contrast only 3 patients (13 %) in C-DM cohort had worsening of glycemic control).
- The Sponsor was advised to apply 95% 2-sided or 97.5% 1-sided confidence intervals. The sponsor applied 1-sided CI instead. Thus, biostatistician reviewer computed 95% 2-sided confidence interval. The lower bound of the 2-sided 95% confidence interval was 16.8%, below the margin, and therefore, not statistically significant.
- The normalization of DBP only, without SBP control might not be clinically meaningful and patients remain hypertensive and carry an overall risk of cardiovascular morbidity and mortality.
- Patients in C-HT cohort had multiple protocol violations including incorrect BP measurements and initiation or change in doses of antihypertensive medications that might affect the blood pressure control at the end of the study. Two of eight patient-responders were also treated with spironolactone that was allowed for the treatment of hypokalemia, but may also decrease BP.
- Lastly, cortisol levels remain elevated during treatment with Korlym, and may activate mineralocorticoid receptors and increase blood pressure. Thus, the antihypertensive effect of Korlym may be less obvious and Korlym may actually worsen BP control.

The changes in bone mineral density, in muscle strength, and in cognitive and psychiatric function and in quality of life (QOL) were inconclusive, most likely because of the small number of evaluated patients, short duration of the treatment and wide range of the baseline and final scores.

Supportive evidence for the efficacy of Korlym is provided by a review of 13 published reports of mifepristone (Korlym) use in 44 patients with Cushing's syndrome which show that mifepristone has benefits in mitigating the effects of high circulating levels of cortisol in patients with Cushing's syndrome. In these studies the majority of patients were treated with therapeutic courses of mifepristone 200 to 2,000 mg/day or 5 to 25 mg/kg/day for up to 24 months and demonstrated a rapid improvement in clinical signs of hypercortisolemia during the first month of treatment, including improvement in somatic features of Cushing's syndrome (buffalo hump, central obesity, moon facies, peripheral edema, striae), psychiatric symptoms, normalization of gonadal and thyroid hormone levels, reversal of heart failure, improved libido, improvement of oral candidiasis, and improvements in muscular weakness, hypertrichosis, and skin hematomas. Some patients had improvements in glycemic control, including reduction in the use of anti-diabetic medications or changing from insulin to oral anti-diabetic drugs.

Safety

Treatment with Korlym at doses of 300 mg to 1200 mg once a day demonstrated an acceptable safety profile in a population of subjects with Cushing's syndrome, as analyzed in Studies 400 and C1073-415 (referred to as "Study 415" in this review), the extension study of Study 400. All 50 patients received at least one dose of Korlym in Study 400, and of these, thirty patients had up to 18 months of cumulative exposure to Korlym in Studies 400 and 415. Twenty-seven of thirty patients are still continuing treatment with Korlym in Study 415. The safety profile of Korlym is mostly anticipated by its mechanism of action, and includes such clinically significant adverse events as adrenal insufficiency, hypokalemia and endometrial thickening; they are largely predictable, can be monitored, treated, and typically resolve with appropriate treatment and/or on cessation of the drug.

- Adrenal insufficiency

Adrenal insufficiency may occur during treatment with Korlym because the drug blocks the biological effect of cortisol at tissue level. Cortisol levels remain elevated during treatment with Korlym and the biochemical diagnosis of adrenal insufficiency is not possible. The diagnosis is therefore based on the presence of suggestive signs and symptoms of adrenal insufficiency such as fatigue, decreased appetite, nausea, hypotension, and hypoglycemia. Adrenal insufficiency usually resolves with drug discontinuation and glucocorticoid supplementation. Adrenal insufficiency was uncommon in Cushing's syndrome studies and was reported by the Sponsor in two patients with Cushing's syndrome. Additionally, two more patients had symptoms suspicious of adrenal insufficiency as judged by this reviewer.

- Hypokalemia

Hypokalemia, edema, hypertension and metabolic alkalosis may occur during the treatment with Korlym due to the activation of mineralocorticoid receptors by excess cortisol. Hypokalemia was a common event in patients with Cushing's syndrome and occurred in up to 44% of subjects; severe hypokalemia ($\leq$ 2.4 mEq/L) occurred only in a few subjects. Hypokalemia was preceded by declining potassium levels in all cases, indicating that close monitoring and early intervention might prevent severe episodes. Hypokalemia improved with treatment with potassium supplementation and mineralocorticoid antagonists.

- Endometrial hypertrophy

Endometrial thickening and bleeding may occur due to the anti-progesterone effect of Korlym on the endometrium and can be monitored by transvaginal ultrasound. Korlym-induced thickening of the endometrium is usually decreased with drug cessation. Increase in endometrial thickening was common in the Cushing's syndrome studies and was reported in up to 30% of females, although only a few of them had vaginal bleeding. Histological changes associated with endometrial thickening were benign and consistent with progesterone-associated endometrial changes observed in women receiving progesterone receptor modulators; no cases of neoplasia were reported in any of patients.

- Pregnancy termination

Because of the well-known antiprogesterone effects of Korlym that results in termination of pregnancy, pregnant patients were not allowed to participate in the study. The overall risk of pregnancy in patients with Cushing's syndrome is low due to infertility and amenorrhea induced by hypercortisolemia. However, additional precautions were taken during both studies: pregnancy tests were performed before enrollment and repeated after any significant interruption

of Korlym treatment, and all female patients were required to use non-hormonal methods of contraception during the studies. No pregnancies were observed in any of the Corcept-sponsored studies.

- Drug-drug interaction

Korlym is metabolized in the liver by the cytochrome P450 (CYP3A4) isoenzyme. Thus, there is a potential for interactions between Korlym and drugs that are substrates for CYP3A4 or interact with the CYP3A4 isoenzyme. CYP3A4 inhibitors may inhibit Korlym's metabolism and increase its serum levels; CYP3A4 inducers may induce Korlym metabolism and lower its serum levels. Concurrent use of Korlym with drugs that are CYP3A4 substrates may increase the plasma concentration of these drugs. Due to the slow elimination of Korlym from the body, drug interactions may be observed for a prolonged period of time after its administration. To prevent drug-drug interactions, discontinuation or dose reduction of such medications may be necessary.

Other adverse events frequently observed in Corcept's studies in patients with Cushing's syndrome are nausea, fatigue, headache, peripheral edema, arthralgia, hypertension, dizziness, decreased appetite, increased thyroid stimulating hormone (TSH) levels and rash. No evidence of Steven-Johnson syndrome or Toxic Epidermal Necrolysis has been reported. All of these adverse events can be mitigated and/or treated by frequent monitoring, timely introduction of appropriate therapy, and discontinuation of the drug. Decline in high density lipoprotein levels (HDL) was noticed in patients with Cushing's syndrome, but was monitored with simple tests and resolved with treatment cessation. The function of the HDL particle (cholesterol efflux) was preserved, as was demonstrated in healthy volunteers. The clinical significance of the decline in HDL-cholesterol levels in patients with Cushing's syndrome is unclear and longer duration of treatment is required to evaluate the impact of the decreased HDL levels on the cardiovascular morbidity and mortality. Korlym has an effect on the QT interval prolongation in animals. No effect of Korlym on QT interval was detected in the human study, although the study was inconclusive and small increase in QTc interval could not be excluded. No clinically meaningful ECG abnormalities were observed in patients with Cushing's syndrome. No abnormal ophthalmological findings related to Korlym use were detected in any of the studies up to date. No clinically meaningful abnormalities in liver function tests (LFT) were found in patients with Cushing's syndrome treated with Korlym for up to 18 months. Lastly, even though subjects with Cushing's disease are at risk for the increase tumor volume due to the increased ACTH production, no clinically meaningful tumor enlargements associated with Korlym treatment were observed in any of the subjects. Longer exposure to Korlym might be required to detect clinically meaningful ophthalmological findings, changes in LFTs and in tumor volume.

Additional supportive safety data for Korlym was provided from the other 27 other studies conducted by Corcept (b) (4) and in healthy volunteers. Over 1200 patients in these studies have received a short course of treatment with Korlym at doses of 50-1200 mg daily. Overall, analysis of safety data of mifepristone in these populations did not differ from the safety findings in patients with Cushing's syndrome.

Lastly, the review of published reports of mifepristone use in 51 patients with Cushing's syndrome did not identify new safety issue with the use of Korlym in patients with Cushing's syndrome, although no formal safety reporting was included in any of the publications. Overt adrenal insufficiency with hypotension was reported in only three patients and hypokalemia in 14 patients.

In conclusion, Korlym treatment for 24 weeks in subjects with Cushing's syndrome resulted in improvements in major co-morbid metabolic abnormality, such as impaired glycemic control, and in other clinical signs and symptoms of Cushing's syndrome resulting from hypercortisolemia. These finding are compatible with the results reported in the literature of the use of mifepristone in Cushing's syndrome. Although surgery remains the treatment of choice for many patients, Korlym is effective in decreasing the clinical impact of hypercortisolemia and improving the patient's clinical status. With careful monitoring, Korlym has an acceptable safety profile for chronic use in patients with Cushing's syndrome.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

In this NDA the Sponsor proposed a REMS with ETASU for Korlym that is intended to minimize the serious risks associated with use of the drug including termination of pregnancy, adrenal insufficiency, hypokalemia, and drug-drug interactions. The Division determined that a REMS is not necessary for the safe and effective use of Korlym in the Cushing's population. The risk of termination of pregnancy in patients with Cushing's syndrome is low since this patient population is unlikely to become pregnant. Such serious risks associated with use of Korlym as risks of adrenal insufficiency, hypokalemia, and drug-drug interactions can be addressed adequately through physician and patient labeling. However, the Division agreed with the Sponsor's proposal to distribute Korlym solely to a "limited number of specialty pharmacies". This should prove more convenient for patients and will facilitate monitoring the use of Korlym to ensure that it is being used in the indicated population.

The requirements for a REMS with ETASU for approval of Korlym was discussed between DRISK and DMEP. DRISK and DMEP agreed that a REMS with ETASU for Korlym would not improve the benefit/risk balance for the intended use (Cushing's) population, and would impose an unnecessary barrier to their access to the drug. The other concern was if a REMS with ETASU is necessary for the approval of Korlym in order to maintain the integrity of the Mifeprex REMS program. The requirement for a REMS with ETASU for approval of Korlym was discussed during REMS Oversight Committee (ROC) meeting on September 29, 2011 and during the meeting with CDER director, Dr. Woodcock on November 3, 2011. The final decision was made that a REMS is not necessary to ensure that the benefits of Korlym outweigh the risks for the treatment of patients with Cushing's syndrome.

1.4 Recommendations for Postmarket Requirements and Commitments

The nature of the postmarketing requirements that may be required of the Sponsor are still under discussion, with the final recommendations to be included in the Approval letter. As discussed later in this review, Sponsor did not evaluate the drug-drug interaction between Korlym and strong CYP3A4 inhibitor, ketoconazole. Interaction of Korlym with ketoconazole is of particular interest, because ketoconazole is an inhibitor of glucocorticoid synthesis and widely used off-label antiglucocorticoid medication. There is likelihood that these drugs may be co-administered when control of hypercortisolemia is not achieved with Korlym treatment only. Thus, Clin/Pharm team recommended implementation of a postmarketing study evaluating the effects of strong and moderate CYP3A4 inhibitor, ketoconazole on Korlym PK.

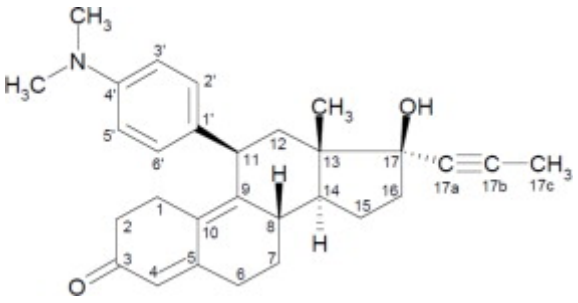
2 Introduction and Regulatory Background

2.1 Product Information

Product Description
Korlym (Mifepristone) contains a single active ingredient, mifepristone. Mifepristone is a potent and specific antagonist of the type II nuclear glucocorticoid receptor (GR-II) and competes with cortisol for the binding to the receptor, preventing biological effect of cortisol. It does not decrease cortisol level. Mifepristone is also selective progesterone receptor antagonist.

Active Substance: mifepristone
Mifepristone is a single enantiomer with 5 chiral centers with the absolute stereochemistry 8S, l1R, 13S, 14S, 17S.

Figure 1. Structural Formula



Chemical formula:
C29H35NO2

Chemical name:
11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(1-propynyl)-estra-4, 9-dien-3-one.

Established name
Mifepristone

Proposed Trade Name
The proposed trade name for mifepristone (also referred to previously as CORLUX or C-1073 in Corcept-sponsored studies) is KORLYM. The Division of Medication Error and Analysis found this proposed name acceptable. For the clarity of this review, Korlym will be referred as Korlym in Corcept's studies in patients with Cushing's syndrome (studies C1073-400 and C1073-415) or as mifepristone in all other Corcept-sponsored studies and in published literature hereafter.

Applicant's Proposed Indication
The Sponsor proposes Korlym to treat clinical and metabolic effects of hypercortisolemia in patients with endogenous Cushing's syndrome, including:

- patients with Cushing's disease who have not adequately responded or relapsed after surgery
- patients with Cushing's disease who are not candidates for surgery

(b) (4)

In the US, it is estimated that approximately 5,000 patients with Cushing's syndrome would be considered candidates for the chronic treatment with Korlym.

Applicant's Proposed Age Groups
Adults (≥ 18 years of age)

Applicant's Proposed Dosing Regimen
The proposed starting daily dose for Korlym is 300 mg administered orally to patients with Cushing's syndrome. The dose may be increased to 600 mg once daily based on assessments of clinical response and tolerability. Further escalation in 300-mg increments to a maximum of 1200 mg once daily may be appropriate in some patients with increased monitoring for risk factors associated with the drug.

2.2 Tables of Currently Available Treatments for Proposed Indications

Endogenous Cushing's syndrome (CS) is a serious, multisystem disorder that results from the overproduction of cortisol by the adrenal glands. The majority of Cushing's syndrome is caused by excessive secretion of adrenocorticotropic hormone (ACTH) (80% of patients). ACTH-dependent Cushing's syndrome is caused most commonly by pituitary adenoma (Cushing's disease (CD)) in 80-85% of patients, and, less often, by ectopic ACTH production by extrapituitary tumors (10%) (Pivonello et al, 2008). Twenty percent of patients with Cushing's syndrome have ACTH-independent disease caused by excessive autonomous cortisol secretion by the adrenal glands: by unilateral adrenal tumor (60%), or less frequently, by adrenal carcinoma, macronodular adrenal hyperplasia, primary pigmented nodular adrenal disease, or McCune-Albright syndrome (Biller et al, 2008; Newell-Price et al, 2006). The incidence of the

Cushing's syndrome ranges from 0.7 to 2.4 per million population per year (Newell-Price et al, 2006). It is estimated that at any given time there are approximately 20,000 patients with Cushing's syndrome in the U.S. Ninety percent of all cases of Cushing's syndrome occur during adulthood; the incidence of Cushing's syndrome in children is estimated at approximately 0.2 cases per 1 million persons per year. The peak incidence of Cushing's syndrome due to pituitary tumor occurs in persons 25-40 years of age; females are 4 times more likely than males to develop hypercortisolemia due to a pituitary tumor.

The clinical manifestations of Cushing's syndrome are variable, ranging from subtle to severe. Some of these manifestations include obesity, myopathy, bone loss, gonadal dysfunction, dermatological changes, compromised immune function, psychiatric disturbances, and fluid and electrolyte disturbances. About 80-90% of patients with Cushing's syndrome have abnormal glucose levels on OGTT, and 20% of them develop overt diabetes mellitus (DM); 70% of patients are diagnosed with hypertension (Bruno, 2010). Cushing's syndrome is associated with decreased quality of life and an increased mortality rate. The mortality rate in patients with Cushing's syndrome is 5-fold higher than in age and gender-matched subjects (Etxabe et al, 1994). Median survival in patients with untreated hypercortisolemia is 4.6 years (Newell-Price et al, 2006). The causes of death in Cushing's syndrome are mainly due to cardiovascular complications; the risk of death is independently increased with co-existing diabetes mellitus and/or hypertension (Clayton et al, 2011).

Because of the significant morbidity of Cushing's syndrome, early and prompt therapy is warranted. In general, surgery is a first line therapy and treatment of choice for all causes of Cushing's syndrome. Surgery is successful in 60-80% patients with Cushing's disease caused by pituitary microadenoma (Pivonello, 2008) and less effective in patients with large and invasive pituitary tumors and in patients with occult or metastatic ectopic ACTH-secreting tumors. Second line therapy of Cushing's syndrome includes radiation therapy, medical therapy, and bilateral adrenalectomy. Pituitary radiotherapy is effective means of treatment of the persisting hypercortisolemia after trans-sphenoidal surgery and controls hypercortisolemia in 45-60% of cases (Vance, 2005), but is associated with long-term panhypopituitarism and its effectiveness can be delayed for years. Bilateral adrenalectomy is indicated when tumor can not be identified and hypercortisolemia is severe and requires prompt control. After adrenalectomy patients need long-life treatment with gluco- and mineralocorticoids; the development of the Nelson's syndrome is a concern in patients with Cushing's disease.

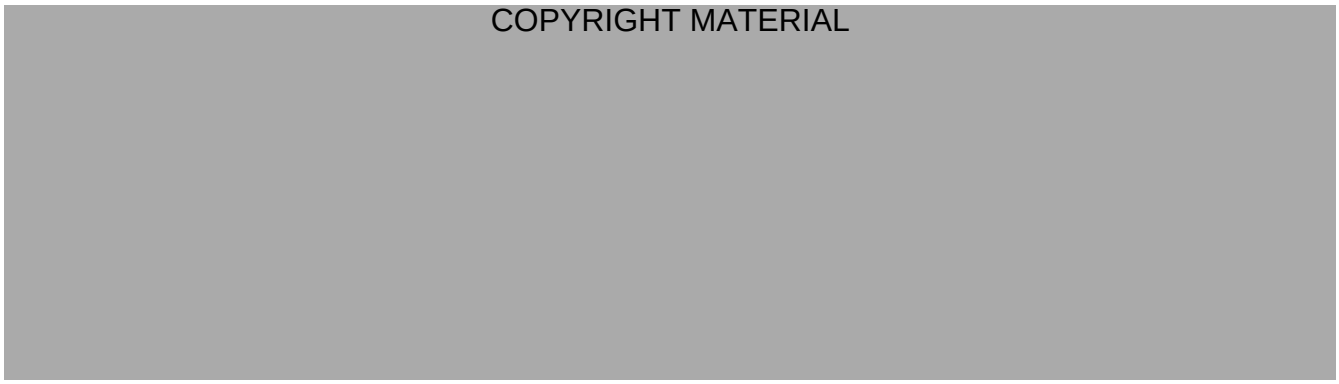
Medical therapy is used when surgery is not effective, in patients with Cushing's disease who undergo radiotherapy to control hypercortisolemia until the results of radiotherapy become effective and cortisol levels are reduced, in patients who are not candidates for radiation or surgery or when immediate control of the hypercortisolemia is required due to the severity of the disease. Lifelong medical treatment to suppress cortisol levels may be required if the primary cause of Cushing's syndrome cannot be treated successfully with surgery and/or radiation. **Currently there are no drugs approved for the treatment of hypercortisolemia in patients with Cushing's syndrome**. Several drugs, in different pharmacological classes have been

widely used **off label or under the investigation** for the treatment of hypercortisolemia in patients with Cushing's syndrome. These compounds work through three mechanisms of action:

- modulation of ACTH release from pituitary tumor (in Cushing's disease),
- steroidogenesis inhibition,
- glucocorticoid antagonism by the blocking of the cortisol action at its receptor.

Compounds that affect ACTH release and/or production include cyproheptadine, retinoic acid bromocriptine, and somatostatin analogs. Overall, all these drugs were evaluated as single therapeutic agents for the treatment of Cushing's syndrome only in small studies; the response rates were poor (Nieman, 2002). Steroidogenesis inhibitors are widely used for treatment of ACTH-dependent and ACTH-independent Cushing's syndrome and include such compounds as ketoconazole, metopirone, mitotane, and etomidate (Table 1). These medical therapies are effective, but can sometimes be associated with side effects that limit their use. In addition, metyrapone is only available in the U.S. for compassionate use. Mifepristone is a progesterone receptor antagonist and also blocks glucocorticoid activity at the level of the type II glucocorticoid receptor (GC-II).

Table 1. Adrenal-blocking Drugs



Feelders et al, Neuroendocrinology 2010;92 (suppl 1).

2.3 Availability of Proposed Active Ingredient in the United States

Mifepristone, as Mifeprex 200 mg tablets, was originally approved in US on September 28, 2000 under NDA 20687 for the medical termination of pregnancy (sponsored by the Population Council) and is currently marketed by Danco Laboratories. The approved dose of Mifeprex for the termination of pregnancy is a single 600 mg dose administered orally (three 200 mg tablets).

2.4 Important Safety Issues With Consideration to Related Drugs

Safety Issues associated with Mifeprex

Korlym shares a common mechanism of action with the only approved product containing mifepristone, Mifeprex. Of note, Mifeprex is given only as a single dose of 600 mg to healthy females. Since the proposed product will be used for the chronic treatment of hypercortisolemia in a different population of patients (with Cushing's syndrome) in higher than approved doses,

thus, it is difficult to extrapolate the safety findings of Mifeprex to the current application. The most serious and sometimes fatal adverse events that are reported with Mifeprex use and have black-box warning in the label are fatal infections and bleeding associated with abortion, although the label indicates that "no causal relationship between the use of Mifeprex and these events has been established". The other common adverse events described with Mifeprex include gastrointestinal symptoms (nausea, vomiting, and diarrhea), fatigue and rash. Drug interactions are also described in the label for Mifeprex. "Mifepristone is metabolized by CYP3A4, thus CYP3A4 inhibitors such as ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit mifepristone's metabolism and increase its serum levels. Inducers of CYP3A4, rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism and lower its serum levels. Concurrent use of mifepristone with drugs that are CYP3A4 substrates may increase serum levels of these drugs. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration, thus discontinuation or dose reduction of such medications may be necessary". Lastly, Mifeprex is contraindicated in patients with chronic adrenal insufficiency.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Between the date of the original IND # 76480 submission and the date of submission of the current NDA (April 15, 2010), there have been multiple communications between the Division of Metabolism and Endocrinology Products (DMEP) and Corcept Therapeutics in the form of emails and written responses to the questions submitted by the Sponsor, all addressing various scientific and regulatory aspects related to the current NDA. Some of the addressed issues are discussed below.

1. On July 5, 2007 Corcept was granted Orphan Designation for the use of Kolrym in Cushing's syndrome.
2. On August 2, 2007, Sponsor submitted the original IND # 76480 for Korlym for treatment of patients with Cushing's syndrome

The Division reviewed the IND and issued the Division's advice /information letter on September 9, 2007 with the following important comments and agreements:

- The Division agreed that a single study with an accompanying review of the literature provides reasonable basis for NDA submission and the open-label design of the study is acceptable
- The Division agreed that the toxicology studies conducted prior to the IND submission and two ongoing carcinogenicity studies will be sufficient under Section 505(b)(2) of the Federal Food, Drug, and Cosmetics Act to bridge this NDA to the nonclinical data in the Mifeprex label and to support the non-clinical portion of the current NDA
- The Division recommended modifying primary and secondary end-points of pivotal study: the primary endpoint should be a change in BP and/or glycemic control. All patients should undergo OGTT for calculation of AUC for glucose and changes in hyperglycemic medications should be taken into consideration. An assessment of composite endpoint of clinical improvement should be the secondary endpoint

- The Division recommended a maximum dose of 20 mg/kg/day to be used in the study based on observation that AUC does not increase proportionally with the dose of mifepristone and there is a small pharmacologic difference despite the significant increases in dose and exposure

3. On September 9, 2009, the Division agreed that a dedicated reproductive study conducted in women and men is not required prior to the submission of the current NDA.
However, Sponsor was recommended to investigate the reproductive safety in females enrolled in Study 400 by endometrial biopsies at baseline and at the end of the treatment The Division also indicated that such studies may still be required at a later time depending on the analysis of the findings of Study 400.
4. On March 5, 2010 the Division reviewed the SAP for Study 400 and issued the following recommendations:
The Sponsor proposed to (b) (4) . The Division recommended to not (b) (4) (b) (4) Sponsor was advised to Sponsor was also advised to use a two-sided 95% confidence interval (CI) or 97.5% one-sided CI for analyzing the primary endpoints.
5. Communications between Sponsor and the Agency regarding ophthalmological risk evaluation
There were multiple communications between February, 2010 and October, 2010 regarding appropriate evaluation of the ophthalmological risk observed in non-clinical studies with the use of mifepristone.

- On February 2, 2010, the Division requested an ophthalmology consult, because retinal atrophy was observed in albino rats after one year of treatment with mifepristone. The ophthalmology consultant concluded that it was difficult to assess whether mifepristone carries additional ophthalmic risk beyond the standard ophthalmic risk for glucocorticoids (cataracts and glaucoma). Thus, the Division recommended incorporating an ophthalmological examination into the Phase III studies (400 and 415). Additionally, the Division recommended conducting comprehensive eye exam in newly enrolled subjects in all trials longer than 6-week duration.
- On July 22, 2010, Sponsor submitted Study C1073-425 protocol and incorporated ophthalmologic monitoring into the study. Study C1073-425 was originally designed to evaluate the effect of a 14-week treatment with 600 mg of mifepristone on HDL levels in healthy volunteers.
- On October 7, 2010, the Division reviewed study 425 protocol and concluded that the 6-week study is not of sufficient duration to adequately monitor for possible ophthalmologic damage associated with mifepristone and that appropriate ophthalmologic monitoring in trials of longer duration is needed.
- On November 16, 2010, Sponsor amended the protocol of the Study 415 (extension study of the safety of Korlym in patients with Cushing's syndrome) by adding the ophthalmological evaluation at entry and every 6 months thereafter. The Sponsor stated that all patients in this study have been previously exposed to Korlym, thus precluding a baseline examination (also discussed in pre-NDA meeting with Sponsor on September 14, 2010).

6. Communications between Sponsor and the Agency regarding evaluation of the risk of HDL reduction

In study 400 a reduction in HDL has been observed in patients with Cushing's syndrome when assessed by standard lipid panels.

- On May12, 2010, Sponsor incorporated lipid evaluation by a specialized lipid assay in study 415 at entry visit, Month 6 and end of study.
- On July 2, 2010 Sponsor submitted study C1073-425 protocol to evaluate the effect of mifepristone on HDL-cholesterol levels in postmenopausal healthy female volunteers taking 600 mg of mifepristone once a day for 14 weeks.

7. On September 9, 2009 and January 4, 2010, the Division denied Sponsor's requests for Fast Track designation for Korlym in the treatment of patients with Cushing's syndrome.

The requests were denied on the basis that the Sponsor had not demonstrated that Korlym affects a serious aspect of this condition.

8. On September 14, 2010, a pre-NDA meeting between the Sponsor and Agency was held to discuss filing of an NDA for IND # 076480.

For specifics, refer to Meeting Minutes in DARRTS under IND # 076480.

The Sponsor's objectives for this meeting were to: (1) gain an agreement on the overall content and format of the NDA; (2) review data the company planned to include in the NDA submission; (3) gain agreement on dataset format to be included in the NDA; (4) obtain feedback on proposed REMS; (5) discuss the content of the 120-day safety update to the NDA; (6) gain agreement on the primary stability data that will be submitted to the NDA. Some of the comments and agreements that were reached during this meeting are as follows:

- For the 505 (b)(2) application Corcept will be cross-referencing the non-clinical data for Mifeprex. The nonclinical toxicology studies conducted under IND #76480 are sufficient to bridge Korlym to the nonclinical findings of safety and efficacy of the Mifeprex label. The efficacy data in the label will be based on data from Study 400 and the safety will be based on the data form Study 400 and the extension study 415. Corcept does not intend to rely on clinical data from the literature for labeling.
- The Sponsor confirmed that the endometrial thickening in women with an intact uterus was evaluated in Studies 400 and 415. However, the Sponsor indicated that the majority of the subjects in Study 400 had already been enrolled in the study by the time the Agency requested to incorporate endometrial biopsies in study 400, thus the endometrial biopsies were performed in a few subjects only. In study 415, all women have ultrasound at 3-month intervals, as well as endometrial biopsies at the beginning and the end of the study.
- The Sponsor provided a response to the Division's request dated March 3, 2010 to evaluate the ophthalmologic risk in all newly enrolled subjects in studies lasting longer than 6 weeks.
- The Sponsor indicated that by the time a retinal exam was requested by the Agency, enrolment in study 400 was almost complete. Incorporation of the retinal exam in study 415 is complicated because all patients in that study have been previously exposed to Korlym, precluding a baseline examination. Therefore, the Sponsor includes the ophthalmological evaluation in 6-week Study 425.
- The Division indicated that the REMS with restricted distribution will be necessary for this NDA/indication to address the risk of termination of pregnancy and to maintain the integrity of the current Mifeprex restricted distribution program.

- The Sponsor and the Agency agreed that the original NDA will include all data from Study 400 and from 20 subjects enrolled in Study 415 who received the drug for an additional period of time from 1 to 12 months. A 120-day update will include the most recent data from these 20 subjects and data on 10 more subjects who are expected to be enrolled in study 415. Additionally, only abbreviated reports for studies of mifepristone in other indications will be submitted. Lastly, only the Summary of Clinical Efficacy and Summary of Clinical Safety will be submitted; separate Integrated Summary of Efficacy and Integrated Summary of Safety are not required for the proposed indication

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, data quality and completeness were adequate to permit review.

3.2 Compliance with Good Clinical Practices

As per Sponsor, all studies were conducted in accordance with the principles of Good Clinical Practice (GCP), with applicable local regulations and with ethical principles laid down in the Declaration of Helsinki. Patients had to sign informed consent prior to receiving study drug and the study protocols had to be approved by Institutional Review Boards.

DSI inspection
The Division of Scientific Investigation (DSI) was consulted on June 27, 2011 to audit the following two sites (Table 2): site #07 and site #08.

Table 2. Research Sites for the DSI audition

Site #, (Name, Address)	Protocol ID	Number of Subjects
Site #07 David Schteingart, M.D. University of Michigan, Division of Endocrinology 1150 W. Medical Center Dr. Ann Arbor, MI 48109	C1073- 400	8
Site #08 Maria Grama Fleseriu, M.D. Oregon Health Sciences University, Endo/Pituitary Unit 3515 SW US Veterans Hospital Road; Portland, OR	C1073-400	8

These sites were selected based on the highest number of study subjects enrolled in Study 400. DSI reviewed the following records: adverse event reporting, inclusion/exclusion criteria, study drug accountability, informed consents, monitoring records, adherence to protocol-specified procedures. The primary endpoint data were verified at both sites, and there was no evidence of underreporting of adverse events. Overall, the DSI conclusion based on results of these inspections was that data submitted by the Sponsor in support of the requested indication should be considered reliable.

The inspection of the Dr. Schteingart's site #07 detected some protocol violations. As per DSI review, these protocol violations were isolated and not likely to impact data integrity. The following important deviations were:
1. Three subjects, two in C-HT cohort (#07-006 and #07-008) and one in C-DM cohort (# 07-004) were started on new antidiabetic and/or antihypertensive medications or had increase in dose of these medications during the study and continued the study. This data is presented in the NDA and listed as a protocol violation or as a concomitant medication.
2. There were multiple protocol violations in blood pressure measurements for efficacy; the difference between two BP measurements exceeded 5 mm HG. The actual blood pressures values obtained at this site were contained in the data listings submitted to the FDA, thus analysis can be performed on the actual blood pressures values.
3. Two subjects (#07-002 and #07-003) were enrolled in the study with the exclusionary high blood pressure readings. This data is presented in the NDA and listed as a protocol violation

The inspection of Dr. Fleseriu's site #08 did not reveal any regulatory violations, the study appears to have been conducted adequately, and the data generated by this site appear to be acceptable in support of the proposed Korlym indication.

Protocol violations in the pivotal Study 400
Thirty-six of 50 subjects had a least one protocol violations (Table 3). All subjects with protocol violations were allowed to enter or continue the study. The majority of protocol deviations involved missing or performing out-of-window study assessments (21 patients), a deviations in BP measurement procedure including the obtaining difference in two BP values of > 5 mmHg (16 patients), administration of the prohibited medications or change in doses of antihypertensive or antidiabetic medications (12 patients).

In this reviewer opinion, such deviations as out-of-window visits most likely do not affect the study analyses. However, such protocol violations as introduction of new antidiabetic antihypertensive medications and/or increase in doses of these medications might affect the analysis of primary endpoints and study conclusions: the improved glucose control and/or BP control might be due to the more aggressive antihypertensive/antiglycemic treatment and not to the Korlym itself.

Table 3. Number (%) of Patients with Protocol Violations

Violations	C-DM	C-HT	Total
Study procedures not performed or performed on the wrong date	13	8	21
Incorrect BP measurements	9	7	16
Administration of prohibited medications, change in the dose of the antihypertensive or antidiabetic medications during the study	9*	4**	12
Violations of the inclusion criteria,	5	6	11
Missed visit or visits outside the schedule windows	5	5	10
Non-compliance with performance of the study procedures or incorrect Korlym dosing schedule^	5^	2^^	7
Korlym dosing is changed by patient		4	4

* The prohibited medications were lipid-lowering drugs, heparin in females with intact uterus, steroids for the treatment of inflammatory diseases; one patient was started on ketoconazole and estrogens during the 6 week follow-up period after the last dose of study drug. Additionally, the dose of insulin and metformin and of antihypertensive medications was increased (1 patient each).
** Doses of antihypertensive drugs were increased in two patients, one patient had increase in spironolactone dose and one patient was started on amiloride for hypokalemia control (only spironolactone was allowed to be started for the hypokalemia control).
^One patient developed rash and was not referred to the dermatologists for the further evaluation.
^^One patient was administered 600 mg of Korlym every other day, the dose was changed later to 600 mg and 300 mg every other day (the pre-defined dose schedule by protocol is 300 mg or 600 mg once a day).

Protocol violations in study 415
As per Sponsor, protocol violation summary was not required for the abbreviated report.

3.3 Financial Disclosures

FDA form 3455 was submitted by the applicant. All investigators were certified to have no conflicts of interest.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to Dr. Ysern, Xavier's CMC review for full details. The final CMC recommendations are pending at time of the review.

Korlym is manufactured as a 300 mg tablet for oral use. Each tablet contains 300 mg of mifepristone. Korlym tablets were developed as immediate release tablets; no sustained or modified release characteristics were required because of the long half-life of mifepristone. Korlym demonstrates a pH-related solubility profile: the greatest solubility is achieved in acidic media (25 mg/mL at pH 1.5) and solubility declines as the pH is increased. At pH values above

2.5 the solubility of Korlym is less than 1 mg/mL. The product will be packaged in 28-count and 280-count bottles.

4.2 Clinical Microbiology

Not applicable, Korlym is not an antimicrobial.

4.3 Preclinical Pharmacology/Toxicology

Refer to Pharm. Tox review by Dr. Patricia Brundage for full details. The final Pharm. Tox recommendations are pending at time of the review.

This 505(b)(2) application for Korlym relies in part on the nonclinical fertility and genotoxicity data in the Mifeprex® label (NDA 20687). The Sponsor and the Agency agreed during the pre-NDA meeting on September 14, 2010 that the nonclinical toxicology studies conducted under IND 76,480 are sufficient under Section 505(b)(2) of the Federal Food, Drug, and Cosmetics Act to bridge this NDA to the nonclinical findings in the Mifeprex label approved under NDA 20-687. Mifeprex was approved for an acute indication and did not include data from chronic toxicity or carcinogenicity studies. Thus, for the chronic indication of Korlym in patients with Cushing's syndrome, chronic toxicity 12-month study in dogs and 2-year carcinogenicity studies in mice and rats have been conducted by Corcept. Additionally, the Sponsor conducted two *in vitro* hERG studies, PK studies in the dog and monkey, pivotal repeat dose toxicology studies in the mouse, rat, and dog, and two *in vitro* genotoxicity studies (bacterial mutation and chromosome aberration) in support of this application.

Non clinical issues relevant to the clinical use of Korlym include the following:

1. Corcept conducted two hERG studies evaluating the effects of mifepristone on the potassium selective IKr current. No effect of parent compound on hERG current was seen in the first study. The second study conducted with parent compound and active metabolites of mifepristone demonstrated a significant inhibitory effect of parent compound and its metabolites on hERG potassium current. Thus, the clinical Thorough QT study in healthy human volunteers was conducted to assess the possible cardiac effects of mifepristone administration (refer to Section 7.4.5).
2. The small, but statistically significant, dose-related prolongation of the QT and QTc-intervals in the mid- (25 mg/kg/day) and high-dose groups (60/40 mg/kg/day) were found in the chronic toxicity dog study. Thus, the Sponsor monitored EKG in the majority of clinical studies of mifepristone and also conducted the Thorough QT (TQT) Study C1073-300 (refer to sections 7.4.5 and 7.3.5).
3. Repeat dose studies up to 12 months duration conducted in rats and mice demonstrated the following findings:

- The reproductive changes were consistent with the known pharmacology of mifepristone as a progesterone and glucocorticoid receptor antagonist.
- The liver and thyroid neoplasms are common tumors in the rat, and occur with drugs such as mifepristone that cause microsomal enzyme induction in rats. The mouse study showed no

increase in any tumors associated with a lifetime of dosing with mifepristone. However, Pharm. Tox reviewer concluded that the relevance of the liver and thyroid tumors observed in rats to humans is equivocal and cannot be excluded. Additionally, chronic administration in dogs resulted in elevated ALT levels and hepatocellular pigmentation at exposures equal to or less than clinical exposure. Signs of hepatocellular toxicity in the mouse were also noted. Based on this data, Pharm. Tox reviewer recommended periodic monitoring of liver transaminases levels in patients exposed to mifepristone for a chronic duration.

- The ophthalmic findings of retinal atrophy were noted in rats and are known to occur in albino animals that are more sensitive to light than pigmented animals. There was no retinal atrophy seen in the l2-month study in beagle dogs, which have pigmented eyes. In the opinion of veterinary ophthalmic experts and the Sponsor, these findings are most likely rodent specific and not likely to be of clinical significance. To further evaluate the effect of Korlym on the retina, the ophthalmological evaluation was incorporated in studies C1073-425 and C1073-415 (refer to Section 7.3.5).

4. *In vitro* studies with rat liver microsomes demonstrated that CYP3A4 is involved in the oxidation of mifepristone, while CYP2B1, CYP2B2 and CYP2C7 may be responsible for the demethylation of mifepristone. In humans, CYP3A4 has been shown to be the only isoenzyme involved in mifepristone metabolism. *Ex vivo* and *in vitro* studies predict that mifepristone may induce the metabolism of drugs that are substrates for the CYP3A and CYP2B enzymes.
5. Corcept repeated two of the genotoxicity studies (bacterial mutation and chromosome aberration), because the preferred methods for those assays had been revised since NDA 20-687 was reviewed. The results of the studies demonstrated that mifepristone did not have any genotoxic potential.

4.4 Clinical Pharmacology

Refer to Clin. Pharm review by Dr. Jee Eun Lee for full details. The final Clin. Pharm recommendations are pending at time of the review.

Clinical pharmacology of Korlym under this submission is supported by 18 clinical pharmacology studies in support of this NDA that include PK and food effect studies in healthy volunteers, PK studies in subjects with hepatic and renal impairment, drug-drug interactions studies and Thorough QT study. Additionally, the data for mifepristone PK from Summary of Approval for Mifeprex was also used. The following excerpts are from Corcept's Clinical and Nonclinical overview, and Clin/Pharm review by Dr. Jee Eun Lee.

4.4.1 Mechanism of Action

Korlym is a selective progesterone receptor antagonist at a low dose and competitively interacts with the progesterone at the progesterone receptor site. Mifepristone affinity to the progesterone receptor is 5-fold greater than that of progesterone. Mifepristone is also a potent and specific antagonist of the type II nuclear glucocorticoid receptor (GR-II) at higher doses and competes with cortisol for binding to the receptor. The affinity of mifepristone and its metabolites RU 42633, RU 42848 and RU 42689 to GR II receptor is 100%, 61%, 48%, and 45%, respectively as

compared to dexamethasone (23%) or cortisol (9%) affinity. The drug does not decrease cortisol level, but prevents the biological effect of cortisol. It also exhibits weak antiandrogenic activity through competitive antagonism. Korlym does not have affinity for the GR-I (mineralocorticoid) receptor. Its high affinity for the glucocorticoid receptor makes it a logical candidate for use in the treatment of hypercortisolemia, which is the cause of the clinical and metabolic manifestations of endogenous Cushing's syndrome. Because of mifepristone's mechanism of action to block glucocorticoid receptors and antagonize the effect of cortisol rather than decrease the level of cortisol, the assessment of efficacy and safety of mifepristone treatment in patients with Cushing's syndrome is challenging.

4.4.2 Pharmacodynamics

The effect of mifepristone on pituitary-adrenal axis was extensively studied in the literature. Mifepristone blocks glucocorticoid receptor type II (GR-II receptor) and significantly increases plasma levels of ACTH and cortisol in a dose- and time-dependent manner by blocking central GRs and antagonizing the negative feedback of cortisol (Johanssen et al, 2007).
In Study 400, Korlym doses of 300, 600, 900 and 1200 mg were administered based on tolerability and clinical response. The dose proportionality of mifepristone PK is non-linear in humans. Therefore, to evaluate the effect of increasing the Korlym dose on Korlym PK and on PD variables and PK/PD relationship the Sponsor performed the exploratory analysis using Korlym's dose increments and PK to evaluate the continuous PD variables including ACTH, serum cortisol, HDL, $AUC_{glucose}$ and $AUC_{insulin}$. The Sponsor concluded that Korlym increments above the 300 mg initial dose led to only small increments in Korlym exposure, although the dose increase translated into larger PD effects. For plasma ACTH, serum cortisol and HDL there was a trend for larger effect at doses of 300 and 600 mg, and for the $AUC_{glucose}$ and $AUC_{insulin}$ there was a biphasic dose responses. The Sponsor speculated that this biphasic response was due to the smaller data sets, particularly at the 300 mg dose, and the variability of the PD variables. Finally, the Sponsor concluded that the therapeutic benefit in Cushing's syndrome patients is increased by increased Korlym exposure, with substantial effects on decreasing $AUC_{glucose}$ and $AUC_{insulin}$; this occurs with relatively small effects on plasma ACTH, serum cortisol and HDL.

4.4.3 Pharmacokinetics

1. Absorption
According to the approved Mifeprex label, mifepristone is rapidly absorbed following oral administration of a single dose of 600 mg, with a peak plasma concentration of 1.98 mg/L occurring approximately 90 minutes after ingestion. Mifeprex Summary basis of approval indicates that the absolute bioavailability of 100 mg of mifepristone is approximately 40%, and increases as the dose decreases: 69% for 20 mg and 72% for 40 mg.
2. Distribution
Mifepristone is extensively bound to the plasma proteins, albumin and α1-acid glycoprotein (AAG). Binding of mifepristone and its three active metabolites to plasma proteins is 99.2%, 98.9%, 97.8% and 96.1%, respectively, and is only slightly concentration-dependent. Mifepristone is highly bound to AAG and approaches saturation at doses of 100 mg. The level of

AAG showed no correlation with exposure following a single dose of 600 mg, while both C_{trough} and $AUC_{0\text{-}24hr}$ were highly associated with AAG following multiple doses of 600 mg, 1200 mg, and 1800 mg. The mean apparent volume of distribution (Vd/F) under fed conditions was approximately 270 L. Mifepristone and its metabolites also cross the blood-brain barrier.

3. Metabolism and elimination of the drug

Mifepristone is metabolized in the liver by cytochrome CYP3A4 and produces three active metabolites. Two of three active metabolites are the product of demethylation (monodemethylated RU 42633 and di-demethylated RU 42848), the third active metabolite (RU 42698) is a product of hydroxylation. The terminal half-life shows large variability, ranging from 31 to 91 hours following oral administration of single dose ranging 300 mg ~ 1800 mg of mifepristone. Ninety percent of mifepristone is recovered in the feces, with biliary excretion as the primary route of elimination; excretion in the urine accounts for less than 10% of the dose.

4. PK of a single and multiple doses of mifepristone (Tables 4 and 5)

Corcept evaluated the PK of single doses (up to 1200 mg) and multiple doses of mifepristone (up to 1800 mg). Time to peak plasma concentration following single 600 mg dose administration was 1 - 2 hours, 2-6 hours and 12-36 hours of parental compound, RU 42633 and RU 42698, and RU42848, respectively (Table 4). Time to peak plasma concentrations after multiple doses administration (600 mg) was 1 - 4 hours, 2 - 8 hours and 7 -15 hours for the parental compound, RU42633 and RU 42698, and RU42848, respectively (Table 5). Mean t1/2 in healthy volunteers was 25 – 43 hours following a single dose and 35 - 90 hours following multiple dose administration. The multiple-dose administration of mifepristone results in a plateau of Ctrough by as early as 5 to 7 days after starting drug. The Sponsor concluded that approximately 12 to 15 days are required for the concentrations to fall to approximately 5% and 14% of Cmax in healthy volunteers receiving drug in the fasted and fed states, respectively.

Mifepristone PK shows nonlinear PK, with a little increase in AUC, Cmax or Ctrough as dose increases above 600 mg.

Table 4. Mifepristone Cmax and AUC following Single Doses of 300, 600, and 1200 mg in Healthy Adults in the Fasted State (Source: Table 44 Clinical Pharmacology Summary)

	Dose Level	**N**	**Mean**	**%CV**	**Min**	**Max**	**Lower 95% CI**	**Upper 95% CI**
Cmax (ng/mL)	300 mg	76	2148	44.5	585	4490	1930	2367
	600 mg	69	2647	40.7	569.6	6158	2388	2906
	1200 mg	46	2853	38.1	667	7030	2530	3176
% increase	300 to 600 mg		23.2					
	600 to 1200 mg		7.8					
AUC (ng*hr/mL)	300 mg	75	65586	53.9	17800	196900	57445	73726
	600 mg	59	129915	55.1	34095	369617	111268	148561
	1200 mg	22	152804	57.2	63168	474486	114079	191530
% increase	300 to 600 mg		98.1					
	600 to 1200 mg		17.6					

Source: Clin/ pahrm review

Mifepristone shows also time dependent PK. Following multiple-dose administration of mifepristone, significant increases in AUCs of all analytes due to the prolonged half-lives have been observed in both healthy volunteers and subjects with moderate hepatic impairment as compared to those following single dose.

Table 5. Summary of Plasma PK Parameters of Mifepristone and its Metabolites following a Single dose of 600 mg or Multiple doses of 600 mg/day of Mifepristone for 7 days (Study C-1073-05)

Analyte	Dosing Regimen	$T_{1/2}$ (hr)	Cmax (ng/mL)	Tmax (hr)[a]	$AUC_{0\text{-last}}$ (ng*hr/mL)	$AUC_{0\text{-inf}}$ (ng*hr/mL)
Mifepristone	Multiple	84.6 (60.9)	3329.3 (1259)	1 [0.5, 2]	323797 (146061)	369177 (205164)
	Single	40.7 (14.6)	2982.3 (1040)	1.25 [0.5, 6]	164816 (60913)	170059 (61717)
RU42633	Multiple	113.1 (87.1)	2165.8 (479.5)	5 [2, 48]	373600 (159271)	473514 (291739)
	Single	45.8 (17.7)	2331.0 (456.2)	4 [1.5, 48]	235378 (78996)	240533 (82669)
RU42698	Multiple	104.3(75.6)	832.4 (362.3)	6 [2, 24]	139791 (77347)	173097 (119240)
	Single	49.5(14.3)	804.1 (291.0)	6 [1.5, 48]	75701 (37773)	79680 (37503)
RU42848	Multiple	123.4(97.7)	1244.0 (367.6)	15 [4, 48]	237523 (96955)	308736 (183913)
	Single	53.3(22.2)	1077.0 (77)	36 [8, 96]	159092 (60058)	167091 (68866)

Source: Clin/pahrm review; [a] Median with range;

7. Food-effect
The fed state increases Cmax and exposure of mifepristone. In the single dose studies, the increases in Cmax and exposure with food were the largest for the 1200 mg dose of (b) (4) The mean Tmax of mifepristone occurs between 1.0 - 2.0 hr when doses of 300, 600 or 1200 mg are administered to the fasted healthy volunteers. Food delays or prolongs absorption of mifepristone; Tmax is increased to 2.9 - 4 hrs when 1200 mg of mifepristone was administered with food. Multiple dosing of (b) (4) at dose 1200 mg/day for 7 days with fat meals showed a mean 65% increase in mifepristone exposure relative to the exposure after 7 days of the drug administration in the fasted state.
8. The Sponsor did not found any association between mifepristone exposure and age, body weight, BMI, and race.
9. The effect of renal impairment on the PK of mifepristone and its metabolites was evaluated in 10 patients with severe renal impairment (creatinine clearance <30 mL/min but not on dialysis) and compared to PK of mifepristone in healthy volunteers (Study C1073-19). All subjects received mifepristone 1200 mg/day for 7 days. The results of the study demonstrated that Cmax and $AUC_{0\text{-}24}$ of mifepristone increased by 30% and 31%, respectively, in subjects with severe renal impairment as compared to healthy volunteers. Cmax and $AUC_{0\text{-}24}$ increased by 50% and 56%, 33% and 35%, and 12% and 6% for RU 42633, RU 42698 and RU 42848, respectively, in subjects with severe renal impairment as compared to healthy volunteers. Median T_{max} for

mifepristone and its metabolites, and plasma protein unbound concentration of mifepristone or RU 42633 were unaffected by renal impairment. The Sponsor concluded that no change in the initial dose of (b) (4) is needed for severe renal impairment, but the maximum dose should not exceed 600 mg per day (refer to Section 7.5.4).

10. Impact of Hepatic Impairment on PK

The effect of hepatic impairment on the PK of mifepristone and its metabolites was evaluated in 10 subjects with moderate hepatic impairment (Study C1073-05). Each subject received a single dose of 600 mg of mifepristone followed by a 7-day regimen of 600 mg/day of mifepristone. The PK parameters were similar after a single and multiple dose administration in both groups of patients with impaired and normal hepatic function (refer to Section 7.5.4). The Sponsor concluded that no dosage adjustment is necessary in patients with mild to moderate hepatic impairment. Clin. Pharm reviewer recommended that, the maximum dose should not exceed 600 mg per day. Mifepristone is mainly metabolized in the liver and three active metabolites demonstrate prolong t1/2 in patients with moderate hepatic impairment. Since the linear increase in exposure is not expected with the dose increase, attempt to match exposure may fail in assurance of efficacy and safety in patients with severe hepatic impairment. Thus, mifepristone should not be used in patients with severe hepatic impairment.

11. Comparison of exposure in patients versus healthy adults

The Sponsor pooled trough mifepristone concentrations across multiple-dose studies and evaluated these concentrations by dose level in patients with Cushing's syndrome and psychotic depression and in healthy adults. The Sponsor demonstrated that there was a difference in Ctrough across the three populations of patients at the 300 mg dose level. Cushing's patients had higher concentrations (1703 ± 867 ng/mL) than the other patients (1349 ± 552 ng/mL and 1173±344 ng/mL in patients with psychotic depression and healthy adults, respectively). At the 600 mg dose level, there was no statistically significant difference in Ctrough across the three populations. At 1200 mg dose level, the Ctrough concentrations were higher in Cushing's patients than in healthy adults (2274±1097 ng/mL and 1770± 582 ng/mL, respectively). The Sponsor concluded that because of the broad overlap in mifepristone Ctrough between the healthy volunteers and Cushing's patients and the inconsistent differences in the concentrations between these two populations, the PK findings in healthy volunteers are generally applicable to Cushing's syndrome patients.

12. Drug-drug interaction studies (DDI)

Briefly, in vitro studies indicated that there is a potential for mifepristone and/or its metabolites to inhibit oxidative drug metabolism mediated via CYP2A6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4, and to inhibit transport via P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Thus, clinical studies in healthy subjects have been conducted to evaluate an interaction between multiple dose of mifepristone and the CYP3A4 substrates simavastatin and alprazolam, the CYP3A inhibitor cimetidine, the CYP2C8/2C9 substrate fluvastatin, and the P-gp substrate digoxin. The Sponsor choice to evaluate CYP3A4 and CYP2C8/2C9 was based on the fact that CYP3A4 is responsible for the metabolism of the largest proportion (over 50%) of drugs on the market, and CYP2C8/2C9 are the next most common isoenzymes involved in drug metabolism. A drug-drug interaction study with a prototypical mild/moderate CYP3A inhibitor, cimetidine (Study C-1073-26) was conducted because mifepristone may initially inhibit and later induce its

own metabolism. Results of DDI studies and labeling recommendations regarding drug-drug interaction are summarized in Section 7.5.5 and in Clin. Pharm review in DARRTS.

5 Sources of Clinical Data

Sources of clinical data in this review are the original NDA submission that includes data from Corcept's studies of mifepristone (Korlym) in healthy volunteers, in patients with Cushing's syndrome and in other indications, the Sponsor's responses to the Agency's requests for information and published literature of mifepristone use in patients with Cushing's syndrome.

5.1 Tables of Studies/Clinical Trials

This review uses clinical data derived from the Sponsor's 29 studies. Table 6 summarizes primary safety and efficacy studies conducted in patients with endogenous Cushing's syndrome, while Table 7 summarizes Corcept's clinical studies (excluding studies conducted in patients with Cushing's syndrome).

Table 6. Corcept's Safety and Efficacy Studies in Patients with Cushing's syndrome

Study identifier	Objective(s) of the Study	Study design	Dosage regimen	N of patients	Population studied	Duration of study/ treatment	Type of study
C1073-400	Evaluate the efficacy and safety in patients with CS	Phase III, open-label, dose-escalation	300-1200 mg	50	Patients with CS	24 weeks	Studies in patients with CS
C1073-415*	Long-term safety	Phase III, open-label, extension of C1073-400	300-1200 mg	30 (at cut-off date^)	Patients with CS	Long-term	Studies in patients with CS
C1073-415* addendum	Ophthalmologic safety	Phase III, open-label, extension of C1073-400	300-1200 mg	20 (at cut-off date^)	Patients with CS	Long-term	Studies in patients with CS

Source: Sponsor's table 5.2, Module 5, volume 1, modified; *Ongoing study.

Table 7. Corcept's Clinical Studies in non-Cushing's syndrome indication / patients

Study identifier	Objective(s) of the Study	Study design	Dosage regimen	N of patients	Population studied	Duration of study/ treatment	Type of study
C1073-22	Evaluate the effects of different formulations on PK of mifepristone (MIFE)	Phase I, open label, randomized	300 mg (tablets from different mfg. lots)	15	Healthy	10 weeks/ 3 SD^	PK
C1073-05	Evaluate the safety and PK of MIFE in subjects with liver impairment	Phase I, open label	600 mg	20	With hepatic impairment (10) and healthy (10)	3 months/ 1 day and 7 days	PK

C1073-12	Compare PK of MIFE under fed and fasted conditions	Phase I, open label, randomized	600 mg	50	Healthy	57 days/ 2 SD	PK
C1073-16	Evaluate the effect of MIFE on PK of fluvastatin (FLU)	Phase I, open label	MIFE*: 1200 mg; FLU: 40 mg	20	Healthy	9 weeks /7 days MIFE; 3 doses FLU	PK/drug interaction
C1073-19	Evaluate the effect of renal impairment on PK of MIFE	Phase I, open label	1200 mg	18	With renal impairment (10) and healthy (8)	11 weeks/ 7 days	PK
C1073-20	Evaluate the effect of food on PK; evaluate effect of different doses on PK of MIFE	Phase I, open label, randomized	300, 600, 1200 mg;	67	Healthy 24 (fed) 22 (fast)	69 days/ 3 SD	PK/DDI
C1073-23	Evaluate the effect of MIFE on PK of digoxin (DIG)	Phase I, open label	MIFE: 1200 mg; DIG: 0.25 mg x 1 day, than 0.125 mg	24	Healthy	39 days/ MIFE: 10 days DIG: 17 days	PK/DDI
C1073-24	Evaluate the effect of MIFE on PK of alprazolam (ALP)	Phase I, open label	MIFE: 1200 mg; ALP: 1mg	16	Healthy	10 weeks/ MIFE: 13 days ALP: 3SD	PK/DDI
C1073-25	Evaluate the effect of MIFE on PK of simavastatin (SIM)	Phase I, open label	MIFE: 1200 mg; SIM: 40 mg	20	Healthy	39 days/ MIFE: 10 days SIM: 3SD	PK/DDI
C1073-26	Evaluate the effect of cimetidine (CIM) on PK of MIFE and of MIFE on PK of CIM	Phase I, open label	MIFE: 300 mg; CIM: 800 mg	22	Healthy	11 weeks/ MIFE: 14 days CIM: 35 days	PK/DDI
C1073-27	Evaluate the food effect on PK of MIFE	Phase I, open label, randomized	1200 mg	24	Healthy	12 weeks/ 15 days	PK/DDI
C1073-300	Evaluate safety and tolerability of therapeutic and supratherapeutic doses of MIFE on ECG	Phase I Part I: tolerance Par 2: double-blind, randomized	Part 1: MIFE: 1800 mg Part 2: MIFE: 600 mg and 1800 mg, Moxifloxacin: 400 mg	195	Healthy men Part 1: 15, Part 2: 180	53 days/ Part 1: 14 days, Part 2: 14 days	Special Safety
C1073-301	Evaluate effect of rechallenge with	Phase I, open-label	150 mg 300 mg	5	Healthy men	39 days/ 7 days	Special safety

	MIFE in subjects who experienced a rash in Study C1073-300, Part 1		600 mg 1200 mg 1800 mg				
C1073-425	Evaluate the effect of MIFE on HDL levels	Phase I, randomized, double-blind, placebo-control	600 mg	30	Healthy women	84 days/ 14 weeks	Special Safety
C1073-99-01	Safety and efficacy	Phase II, open-label, parallel group	50 mg 600 mg 1200 mg	33	Patients with MDD**	UN ^^ / 7 days	Studies in other indications
C1073-02	Safety and efficacy	Phase III, randomized, double-blind, placebo-control	600 mg	208	Patients with MDD**	56 days / 7 days	Studies in other indications
C1073-03	Safety and efficacy	Phase III, randomized, double-blind placebo-control	600 mg	221	Patients with MDD**	56 days/ 7 days	Studies in other indications
C1073-04	Follow-on study for repeat treatments of patients from studies C1073-02, C1073-03	Phase III, open-label	600 mg	28	Patients with MDD**	28 days/ 7 days	Studies in other indications
C1073-06	Safety and efficacy of 3 dose levels plus antidepressants	Phase III, randomized, double-blind placebo-control	300 mg 600 mg 1200 mg	443	Patients with MDD**	56 days/ 7 days	Studies in other indications
C1073-07	Safety and efficacy	Phase III, randomized, double-blind placebo-control	600 mg	258	Patients with MDD**	56 days/ 7 days	Studies in other indications
C1073-09	Safety and efficacy	Phase III, randomized, double-blind, placebo	600 mg	247	Patients with MDD**	56 days/ 7 days	Studies in other indications
C1073-10	Follow-on study for repeat treatments of patients from studies C1073-06, C1073-07	Phase III, open-label	600 mg	87	Patients with MDD**	56 days/ 7 days	Studies in other indications
C1073-13	Follow-on study for repeat treatments of pts from study 09	Phase III, open-label	600 mg	104	Patients with MDD**	56 days/ 7 days	Studies in other indications
C1073-71	Safety and efficacy	Phase II, randomized, double-blind placebo-control	300 mg	81	Alzheimer's disease	20 weeks/ 16 weeks	Studies in other indications
C1073-200	Efficacy and safety in the prevention of olanzapine-induced weight gain	Phase II, randomized, double-blind placebo-control	MIFE: 600 mg; Olanzapine: 5-10	15	Healthy men	7 weeks/ 3 weeks	Studies in other indications

			mg				
C1073-200-I	Efficacy and safety in the prevention of olanzapine-induced weight gain	Phase II, randomized, double-blind placebo-control	MIFE: 600 mg; Olanzapine: 5-10 mg	59	Healthy men	6 weeks/ 2 weeks	Studies in other indications
C1073-205	Efficacy and safety in the prevention of risperidone-induced weight gain	Phase II, randomized, double-blind placebo-control	MIFE: 600 mg; Risperidone: 0.5 -2 mg	76	Healthy men	56 days/ 28 days	Studies in other indications

Source: Sponsor's table 5.2, Module 5, volume 1, modified; * Mifepristone; ** MDD: Major depressive disorder with psychotic features; ^SD=single dose; ^^UN=unknown

Corcept conducted two open-label studies in patients with Cushing's syndrome:

- Study C1073-400 is the pivotal Phase III study (hereafter referred to as Study 400).
- Study C 1073-415 (hereafter referred to as Study 415) is an extension to Study 400 and evaluates long-term safety of Korlym in patients with Cushing's syndrome.

Corcept conducted 11 Phase I open-label clinical pharmacology studies of mifepristone in healthy volunteers, including:

- Single and multiple dose studies
- PK studies evaluating PK of mifepristone in patients with renal and liver impairment
- PK studies of various formulation of mifepristone
- Drug-drug interactions with PPI, digoxin, simvastatin, alprazolam,

Corcept conducted 13 supportive Phase II and III safety and efficacy studies of mifepristone in the other indications (Alzheimer's disease, major depressive disorder with psychotic features (MDD), and prevention of antipsychotic-induced weight gain):

1. The Phase II studies include 5 studies:

- One open-label study in patients with major depressive disorder with psychotic features (MDD)
- One study in patients with Alzheimer's disease (double-blind, randomized)
- Three double-blind, placebo controlled studies in healthy volunteers evaluating efficacy and safety of mifepristone in prevention of antipsychotic medications-induced weight gain

2. The Phase III studies included 8 studies in patients with MDD, 5 studies were double-blind, placebo controlled and two studies were open-label studies.

Additionally, Corcept conducted three double-blind, placebo-controlled Phase I studies in healthy volunteers of special interest evaluating the effect of mifepristone on HDL-cholesterol levels, on QT interval, and on the reoccurrence of rash in subjects who experienced a drug-related rash in QT study.

5.2 Review Strategy

This review primary focuses on the two clinical studies in patients with Cushing's syndrome: pivotal study 400 evaluating efficacy and safety of Korlym in patients with Cushing's syndrome and extension study 415, evaluating long-term safety of Korlym in the intended population. These studies were reviewed individually.

The efficacy review focused on the single pivotal Phase III study - Study 400. An independent review was performed by biostatistician Dr. Choudhury, Japobrata; please refer to the statistician's review. Additional supportive evidence for the efficacy of Korlym in patients with Cushing's syndrome is obtained from the review of published literature of the use of mifepristone in patients with CS (refer to sections 6.1.10 and 9.1).

For the safety evaluation, emphasis was placed on the studies conducted in patients with Cushing's syndrome: Study 400 and Study 415. The data derived from the other 27 Corcept's studies and from published literature of mifepristone use in patients with Cushing's syndrome were used as the supportive evidence only for the safety use of Korlym. Lastly, the data derived from the three special safety Phase I studies evaluating effect of mifepristone on HDL-cholesterol (Study C1073-425, hereafter referred to as Study 425), QT interval (Study C1073-300, hereafter referred to as Study 300) and reoccurrence of the drug–related rash (Study 301, (hereafter referred to as Study 301) and safety data from 4- month safety update were also analyzed and included in the appropriate sections.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study C1073-400 (Study 400)

Study Title:
An Open-label Study of the Efficacy and Safety of Korlym in the Treatment of the Signs and Symptoms of Endogenous Cushing's Syndrome

Study center(s) and study period:
Twenty US centers participated in the study from August 12, 2008 to January 10, 2011.

Primary Objective:
To evaluate the safety and efficacy of Korlym in the treatment of the signs and symptoms of endogenous Cushing's syndrome.

Secondary Objectives:
1. To assess the efficacy of Korlym on signs and symptoms of Cushing's syndrome as evaluated by the Data Review Board (DRB)
2. To assess the efficacy of Korlym on the $AUC_{glucose}$ changes or use of antidiabetic medications
3. To evaluate the effect of Korlym on HbA_{1C}
4. To evaluate the effect of Korlym on body weight

5. To assess the efficacy of Korlym on the diastolic (DBP) and systolic blood pressure (SBP)or use of antihypertensive medications in all patients
6. To evaluate the safety profile of Korlym by:

- physical examination and vital signs
- standard hematology and chemistry laboratories
- ECG
- Thyroid stimulating hormone (TSH) and free T4, ACTH, serum cortisol, nocturnal salivary cortisol, and 24-hour urinary free cortisol (UFC)
- transvaginal ultrasound (TVUS), and endometrial biopsies
- pituitary tumor size evaluated by magnetic resonance imaging (MRI) in subjects with CD
- adverse events at each visit

Design:
This was a Phase III, 24-week duration, open-label, non-comparative, multicenter clinical study involving 50 subjects with endogenous Cushing's syndrome.

The study consisted of 3 periods:
1.Screening period - up to 6 weeks
2.Treatment period - up to 24 weeks
Patients were followed weekly during the first two weeks of the treatment, and bi-weekly thereafter during the first 3 months of treatment. After the first 3 months of the treatment patients were evaluated monthly or as needed.
3. Follow-up period – up to 6 weeks
The duration of follow-up period was allowed to be reduced if patient was enrolled in study 415 and /or could not tolerate 6 weeks off treatment for Cushing's syndrome.
All treatments and study evaluations were conducted in outpatient settings.

Treatment Groups:
The study had no control group; it was baseline-controlled for the efficacy analysis.
The Sponsor claimed that no control groups were selected because there is no approved comparator drug that is available commercially. All subjects were assigned to receive Korlym beginning at dose 300 mg and escalating the dose as described below.

Medical Officer's Comment:
The conducting of non-randomized study is subject for the type I error and may introduce selection bias.

Doses
All subjects were assigned to start treatment with Korlym at 300 mg once daily. Because of the glucocorticoid-receptor blocking action of Korlym the optimal dose of Korlym in patients with Cushing's syndrome can not be determined through evaluation of cortisol or ACTH concentrations (refer to Section 4.4.1). Thus, clinical signs and symptoms of safety and efficacy were monitored in order to titrate Korlym dosing, and to avoid adrenal insufficiency. The Investigator was encouraged to escalate the dose to the highest level allowed by the protocol,

however, dose escalation was not required if significant clinical improvement was seen. The first dose escalation occurred in 14 days after the initiation of the treatment with Korlym; dose titration occurred in 300-mg increments monthly thereafter based on efficacy and safety. The 300-mg dose increments were chosen because the study used a 300-mg Korlym tablet.

Dose changes (Table 8)
1. Dose was escalated beyond 300 mg if no clinical improvement had been seen and drug was well tolerated.
2. Dose was allowed to be increased above 1200 mg once a day in subjects > 60 kg (or above 900 mg in subjects < 60 kg, based on subject's weight at escalation visit) in case of severe hypercortisolemia. Of note, the Sponsor stated that no patients received more than 1200 mg of Korlym daily.
3. The maximum dose was not allowed to be increased above 20 mg/kg per day.
4. Dose was decreased if improvement was seen or adverse events (AE) developed.
Dose was allowed to be increased after the resolution of AEs
5. Dosing had to be stopped in case of:
- adrenal insufficiency (dose had to be interrupted for at least 7 days)
The drug was allowed to be resumed at dose 300 mg/day for 2 weeks and, then, the dose could be increased as needed, but not above the level where adrenal insufficiency occurred
- vaginal bleeding
The drug was allowed to be resumed if results of endometrial biopsy results were nonpathological (as stated by the Sponsor).

Table 8. Korlym Dosing Regimen

	Escalation visits			
Subject Weight	**Day 1**	**Day 14**	**Week 6**	**Week 10***
< 60 kg	300 mg	600 mg	900 mg	900 mg
≥ 60 kg	300 mg	600 mg	900 mg	1200 mg

Source: Sponsor's table 1, Module 5, vol. 31, CSR 400, p. 24
*Dose escalation stopped at Week 6 for subjects weighing < 60 kg

Patient Population:
Patients 18 years of age or older with diagnosis of endogenous ACTH-dependent or ACTH-independent Cushing's syndrome whose physician determined that medical treatment was needed to control symptoms or signs of hypercortisolemia were eligible to participate in the study. Prior to the enrollment, Investigators had to verify each subject's diagnosis of endogenous Cushing's syndrome by reviewing clinical history and appropriate laboratory data. Eligible subjects had to meet the following inclusion criteria:
1. Had Cushing's disease that did not respond adequately to surgical treatment (recurred or persisted) or radiation treatment for Cushing's disease, or were not candidates for surgery and whose diagnosis was supported by at least one of the following:
    - documentation of ACTH immunoreactivity on a pathological evaluation of pituitary tissue from a previous surgical specimen

- inferior petrosal sinus sampling (IPSS) with a central-to-peripheral gradient (ratio) of > 2 before or > 3 after corticotrophin-releasing hormone (CRH) administration prior to or after pituitary surgery and/or radiation

2. Had ectopic ACTH-producing or ectopic CRH-producing tumor, adrenal adenoma, adrenal carcinoma or adrenal autonomy
3. Had documented evidence of elevated UFC above the limit of normal on at least two complete 24-hour urine collections within 4 months of the baseline visit. At least one elevated UFC must have been obtained during the screening period. Additional collections during the screening period were allowed. Urine collections must have had urinary creatinine measurements to confirm adequate collection.
4. Had at least one of the following:
   - Diabetes mellitus type 2 or impaired glucose tolerance
     - **Diabetes mellitus (DM) defined as** fasting plasma glucose of ≥ 126 mg/dL on two episodes or a 2-hour plasma glucose level of ≥ 200 mg/dL after a 75-g oral glucose tolerance test (OGTT). Lower glucose values were allowed in subjects with a diagnosis of DM who were being treated with antiglycemic medications.
     - **Impaired glucose tolerance (IGT) defined as** 2-hour plasma glucose level 140 mg/dL - 199 mg/dL after a 75-g OGTT.
   - Hypertension defined as a systolic blood pressure ≥ 140 mmHg **and/or** diastolic blood pressure > 90 mmHg or pharmacologically treated hypertension caused by or aggravated by hypercortisolemia.

The following treatment changes were prohibited during the study:
- Initiation of new antihypertensive medications in hypertensive cohort (C-HT)
- Initiation of new antiglycemic medications in DM cohort (C-DM)
- Increase in dose of any of antihypertensive (C-HT cohort only) or antidiabetic medications

The initiation of the new antidiabetic or antihypertensive treatment or increase in the dose of these drugs was prohibited from 2 (for antihypertensive medications in C-HT group) or from 4 weeks (for antidiabetic medications) prior to the administration of the first dose of the study drug till the end of the study. The screening period was used to stabilize treatment with antihypertensive or antiglycemic medications. Subjects had to be removed from the study if they required additional antidiabetic or antihypertensive medications (C-HT group only) or increase in doses of these medications.

5. Had two or more of the following signs or symptoms related to hypercortisolemia
- Cushingoid appearance (moon facies, dorsalcervical 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

7. Had a life expectancy of at least 6 months

8. Had a negative serum pregnancy test, were willing to use non-hormonal methods of contraception, and would not use systemic estrogens during the study and within 6 weeks prior to study entry.

Exclusion criteria:

1. History of *de novo* Cushing's disease
2. History of a factitious hypercortisolemia
3. History of Pseudo-Cushing's syndrome. Subjects with suspected Pseudo-Cushing's syndrome, such as those with severe obesity, major depression, or history of alcoholism, were to undergo a dexamethasone-CRH test. A cortisol value ≤ 1.4 mcg/dL was considered consistent with Pseudo-Cushing's syndrome.
4. Exclusion of patients requiring specific treatments with:

- adrenostatic or neuromodulator medications, including metyrapone, ketoconazole, fluconazole, aminoglutethimide, etomidate, serotonin antagonists (eg, cyproheptadine, ketanserin, or retanserin), dopamine agonists (bromocriptine, cabergoline), gamma aminobutyric acid (GABA) agonists (sodium valproate), somatostatin receptor ligands (octreotide, pasireotide, lanreotide) from 1 month prior to the baseline visit through the end of the study.
  Of note, subjects with adrenal carcinoma who had been receiving stable doses of mitotane for at least 1 month before study entry could continue to receive the same or lower dose for the duration of the study.
- medications that had a large first pass metabolism mediated by CYP3A4 and which have a narrow therapeutic margin and/or are CYP3A4 inhibitors, including cyclosporine, tacrolimus, or sirolimus, HIV protease inhibitors, non-nucleoside reverse transcriptase inhibitors, kinase inhibitors (except sorafenib), simvastatin, lovastatin, atorvastatin, midazolam, triazolam, alprazolam, itraconazole from 14 days prior the baseline visit through the end of the study
- antiresorptive bone active drug, such as bisphosphonate, selective estrogen receptor modulator (SERM), or calcitonin within 6 months of screening. Subjects who had been on antiresorptive treatment > 6 months could have been enrolled.
- anabolic bone agents (teriparatide or strontium) within 6 months of screening and during the study (through the 6-Week follow-up visit).
- proliferator-activated receptor gamma (PPARγ) agonist drugs (thiazolidinediones) from 4 months prior to the baseline visit through the end of the study (6-Week follow-up visit).
- new antidepressant therapy with selective serotonin reuptake inhibitor [SSRI] or tricyclic compound from 6 weeks prior to the baseline visit through the end of the dosing period of the study or increase in dose of these medications.
- new lipid-lowering medications or dose changes of any lipid lowering drug from 4 weeks prior to the baseline visit through completion of the study (6-Week follow-up visit). Subjects who changed from a prohibited statin drug to an allowed statin must have remained on the new statin for at least 4 weeks prior to the baseline visit.

5. Exclusion of patients with concomitant disease such as:

- history of allergic reaction or intolerance to mifepristone
- poorly controlled diabetes mellitus (defined as $HbA_{1C} \geq 11\%$ at screening)

- poorly controlled hypertension (defined as systolic blood pressure > 170 mmHg or diastolic blood pressure > 110 mmHg at screening)
- history of unexplained vaginal bleeding within 12 months of screening in postmenopausal women with an intact uterus. Those who had a gynecological evaluation were excluded from participation if they received a diagnosis of endometrial hyperplasia, endometrial carcinoma, or endometrial polyps
- endometrial abnormalities on transvaginal ultrasound that met one of the following criteria: free fluid pocket of > 4 cm, endometrial thickness > 5 mm and/or ovarian cyst(s) > 2 cm in postmenopausal women, endometrial thickness > 20 mm and/or ovarian cyst of > 5 cm in premenopausal women
- hemorrhagic disorder or treatment with an anticoagulant in women with an intact uterus

6. Exclusion of patients with laboratory abnormalities:

- uncorrected hypokalemia (potassium level of < 3.5 mEq/L). Subjects should have had hypokalemia corrected prior to the baseline visit. Spironolactone was allowed to control hypokalemia but not to be started to manage elevated blood pressure (BP)
- uncontrolled, clinically significant hypothyroidism or hyperthyroidism
- renal failure (defined as serum creatinine ≥ 2.2 mg/dL)
- elevated bilirubin > 1.5 x the upper limit of normal (ULN), elevated ALT or AST ≥ 3 × ULN

Medical Officer's comments:
The inclusion and exclusion criteria are reasonable. The Sponsor decreased the chance of enrolling patients with cyclic Cushing's syndrome by obtaining UFC more than one time prior to the treatment initiation. The Sponsor appropriately prohibited use of medications that are metabolized by cytochrome CYP3A4 and which are CYP3A4 inhibitors.
Other comments are:

1. *The eligibility of the patients to participate in the study was based on the subjective physicians' decision about the severity of the hypercortisolemia that warrant the medical treatment. Thus, patients with less severe disease may have been enrolled in the study. However, there is no correlation of high UFC levels with the disease severity.*
2. *The Sponsor stated that UFC had to be elevated only above normal value; thus by Sponsor's definition, patients with minimally elevated UFC may be candidates for the study. The enrollment of patients with UFC values > 4 x UNL would be more appropriate, because UFC values > 4 x ULN are confirmatory for Cushing's syndrome (Nieman et al, 2008). Enrollment of the patients with high probability of Cushing's syndrome confirmed by the other evidences such as failed surgery or confirmatory pathology results of ACTH staining of the tumor and elevated UFC values just above the normal range is appropriate. Patients in general population with suspected Cushing's syndrome might need higher levels of UFC and/ or other tests for the diagnosis confirmation.*
3. *One of the main inclusion criteria was a diagnosis of hypertension defined as a systolic blood pressure ≥ 140 mmHg and/**or** diastolic blood pressure > 90 mmHg, thus patients with normal DBP (but elevated SBP) were eligible for the study. It would be more relevant to include patients with elevated both, SBP and DBP, and to evaluate the overall BP control by Korlym. Thus, further decrease of normal DBP without SBP control might*

not be clinically meaningful and interpretation of the improvement of the overall hypertension by the decrease in DBP value only in these subjects might be challenging.

4. *The Sponsor allowed patient who were treated with mitotane to continue treatment with the drug throughout the study. Mitotane inhibits steroidogenesis by the inhibition of 11-beta-hydroxylase and cholesterol side-chain cleavage enzymes, decreases cortisol synthesis and, thus, may improve hypercortisolemia by itself. Most likely treatment with mitotane did not affect hypercortisolemia in the enrolled patients; they were treated with stable dose of the drug for > 1 month prior to the onset of treatment with Korlym and remained symptomatic in spite of the mitotane treatment. Thus, treatment with mitotane most likely did not contribute to the improvement in hypercortisolemia during the treatment with Korlym.*

Withdrawal /Discontinuation Criteria

1. Adrenal insufficiency:

Korlym had to be suspended in all cases of suspected adrenal insufficiency that based on the development of the clinical symptoms characteristic of adrenal insufficiency that include malaise, fatigue, lethargy, weakness, anorexia, nausea, vomiting, abdominal pain, altered mental status, hypoglycemia, hyponatriemia, hyperkaliemia and hypotension. Treatment with Korlym could be resumed if the potential benefits outweighed the risks.

2. An increase in the dose or the initiation of new medications for the treatment of impaired glucose tolerance/diabetes in subjects enrolled in C-DM cohort.

3. An increase in the dose of a concomitant medication or the initiation of a new medication for the treatment of hypertension in subjects enrolled in only C-HT cohort; an increase in the dose of antihypertensive medications was allowed for the subjects who were enrolled in C-DM cohort but also had concomitant hypertension.

3. Requirements for one of the excluded medications: metyrapone, ketoconazole, fluconazole, etomidate, serotonin antagonists, dopamine agonists, GABA agonists, octreotide, systemic estrogen, anabolic bone agents, PPARy agonists, simvastatin, lovastatin, atorvastatin, and fluvastatin.

4. Development of a clinically significant drug rash.

5. Development of severe (≤ 2.5 mEq/L) and/or persistent hypokalemia that did not respond to replacement with potassium. The Korlym dose was allowed to be decreased by one dose step if daily oral potassium replacement was insufficient.

7. Vaginal bleeding in an amenorrheic premenopausal woman or any vaginal bleeding in a postmenopausal woman after start of study drug. Reinitiation of Korlym therapy was allowed in women with nonpathological findings on endometrial biopsy.

8. Pregnancy

Endpoints:

Primary efficacy endpoint

There were two primary efficacy endpoints in the study. The endpoints were based on the assessment of glucose or blood pressure changes from baseline to Week 24:

1. For subjects with diabetes mellitus (or impaired glucose tolerance) (C-DM cohort) the primary end point was a change in the area under the concentration-time curve for glucose ($AUC_{glucose}$) during the 2-hour OGTT.
A responder analysis using the modified Intent-to- Treat (mITT) population was used to measure success on this primary efficacy endpoint. Subjects who had ≥ 25% decrease in $AUC_{glucose}$ from baseline to Week 24 were defined as responders. This efficacy measurement was to be declared successful if the lower limit of the exact 95% binomial confidence interval for the responder rate was ≥ 20%.
2. For subjects with hypertension (C-HT) but without diabetes or impaired glucose tolerance the primary endpoint was a change in mean diastolic blood pressure.
A responder analysis of the reduction in diastolic blood pressure from baseline to Week 24 was performed for the mITT population. Subjects who had ≥ 5 mmHg decline in diastolic blood pressure from baseline to Week 24 were defined as responders. This efficacy measurement was to be declared successful if the lower limit of the exact 95% binomial confidence interval for the responder rate was ≥ 20%.

Medical Officer's comments:
1. The glucose control was evaluated by $AUC_{glucose}$ during the OGTT. The OGTT may be affected by multiple factors including diet, exercise, and stress. HbA_{1C} is more relevant measure of glycemic control and recommended by American Diabetes Association (ADA) for the monitoring of effectiveness of the antiglycemic therapy (Standards of medical care in diabetes, 2011). The change in HbA_{1C} levels were evaluated during the study as a secondary efficacy endpoint. Thus, $AUC_{glucose}$ changes supported by HbA_{1C} changes reliably evaluate the overall glycemic control in these patients.
2. The Sponsor evaluated a decrease in DBP by 5 mm Hg or more, but not normalization of DBP. Moreover, the Sponsor evaluated control of DBP only, and not of both, SBP and DBP. Lastly, the Sponsor evaluated decrease in DBP in some patients with normal DBP at baseline (patients with normal DBP (and elevated SBP) were categorized as hypertensive patients and were enrolled in the study). Thus, it is unclear what additional clinical benefit of further decrease of already normal DBP or of the DBP only may be achieved in these patients.

Secondary efficacy endpoints:
The key secondary efficacy endpoint was change the in signs and symptoms of Cushing's syndrome. A Data Review Board (DRB) evaluated signs and symptoms of Cushing's syndrome by eight clinical parameters and by laboratory findings. The following parameters were evaluated:

- assessment of glucose homeostasis
- assessment of blood pressure
- assessment of lipids
- assessment of weight and body composition
- clinical scoring and appearance (acne, hirsutism, striae, Cushingoid appearance)
- strength assessment
- psychiatric and quality of life assessment

- metabolic bone assessment

The evaluation was performed after the 46 subjects (mITT population) had completed the study: the DRB evaluated all available data obtained at baseline, Week 6, 10, 16, 24, and 6-Week follow-up Visits. All three members of DRB were blinded to the dose patients received and to the sequence in which the visits occurred. Each DRB member assigned an overall score of -1 (worsened as compared to the baseline), 0 (unchanged), and +1 (improvement) for each subject at each visit. Subjects whose median score (calculated from the three reviewers' scores) was +1 were defined as responders.

Other secondary efficacy endpoints:

- $AUC_{glucose}$ changes or change in antidiabetic medications evaluated by responder analysis.
- HbA_{1C} in C-DM group at the last visit as a percent change from baseline
- Diastolic blood pressure or change in antihypertensive drugs evaluated by responder analysis.
- Systolic blood pressure change in both cohorts measured at last visit and compared to baseline values
- Body weight at the last visit as a percent change from baseline

Exploratory efficacy variables:

- Waist circumference at every study visit
- Body composition including total and percent body fat, total body lean, trunk fat, percent trunk fat, trunk lean, leg fat, percent leg fat, leg lean, android fat, percent android fat, android lean, gynoid fat, percent gynoid fat, android/gynoid ratio, trunk/leg ratio at screening and Week 24 visits
- Bone mineral density (DXA) measured at lumbar spine, total hip and femoral neck at screening and Week 24 visits
- Bone metabolism markers (osteocalcin, urinary N-telopeptide of type I collagen (NTx), bone specific alkaline phosphatase) at screening and Week 24 visits
- Insulin levels obtained during the 2-hour OGTT evaluated by AUC for insulin ($AUC_{insulin}$). Subjects taking insulin and those not taking insulin were evaluated separately. Homeostatic model of insulin resistance [HOMA-IR] was analyzed
- Muscle strength measured by sit-to-stand test and hand-grip test
- Cognitive and psychiatric assessments evaluated by Beck Depression Inventory-II and Trail Making Tests
- Quality of life evaluated by the Short Form (SF)-36 Health Survey version
- Thombin-antithrombin (TAT), e-selectin, and adiponectin levels

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Medical Officer's Comments:
TAT is a coagulation factor. E-selectin is an adhesion molecule that mediates neutrophils, monocytes, and memory T-cell adhesion to endothelial cells and may play a role in cardiovascular disease. Adiponectin is a hormone secreted by adipose tissue and is inversely related to insulin resistance. The production of these factors is regulated by glucocorticoids. The Sponsor speculated that these markers may provide surrogate markers of cortisol function, and may provide additional information regarding the risks of cardiovascular

morbidity and thrombotic events associated with Cushing's syndrome. There are few data on the usefulness of these biomarkers in Cushing's syndrome; thus they are exploratory variables only.

Pharmacokinetics variables:

- Korlym, Korlym metabolites and AAG serum levels were obtained prior to the each injection of the study drug (C_{min}) on Day 14, and at Week 6, 10, 16, and 24 visits.

Safety was assessed by:

- Adverse events at each study visit
- Clinical laboratory values, including hematology, serum chemistry, and renal profile and liver function tests (LFT) evaluated at each visit.
- Lipid panel evaluated at screening, Day 14, Week 6, 10, 16, 24 and follow-up visits.
- Physical examination and vital signs evaluation. Full physical examination was conducted at screening and follow-up visits; a limited physical examination (general appearance, head, ears, nose and throat, respiratory, cardiovascular, musculoskeletal systems and skin) was conducted at each visit.
- ECG evaluated at screening, Day 14 and 6-Week follow up visits.
- TSH and free T4 evaluated at screening, Week 24 and 6-Week follow-up visits.
- ACTH, serum cortisol, nocturnal salivary cortisol, and 24-hour urinary free cortisol (UFC) evaluated on Day 1, 14, Weeks 6, 10,16, 24 and 6-Week follow-up visits (UFC collection was not required on Day14).
- Serum pregnancy test was obtained at screening and urine pregnancy test was obtained on Day 1 in all females of child-bearing age.
- Pituitary tumor size evaluated by MRI in subjects with pituitary-based disease at Week 10 and 24 visits or as needed
- Transvaginal ultrasound and endometrial biopsies at screening, Week 24 and 6-Week follow-up visits (biopsies were initiated after Amendment 4).

Medical officer's comment:
A salivary cortisol was collected at midnight only in few patients; the majority of patients had the collection of salivary cortisol during the daytime. Thus, the levels of salivary cortisol are not reliable and may reflect not the true degree of hypercortisolemia.

Statistical Analyses
Please, refer to the biostatistician's review for the details.

The primary efficacy analysis evaluated subjects with Cushing's syndrome with two principle complications: those who had DM or impaired glucose tolerance and those who had a diagnosis of hypertension. The efficacy analysis evaluated a percent change in $AUC_{glucose}$ obtained from 2-hr OGTT in subjects with diabetes or impaired glucose tolerance, and the change in mean DBP in subjects with hypertension at Week 24/early termination (ET) from baseline. If no $AUC_{glucose}$ value or BP values was available at Week 24 visit or the last observation occurred > 14 days

after the last dose of the study drug the most recent previous values were used. The choice of the 14-day period was based on the half-life of Korlym; the Sponsor stated that 14 days exceeds the expected duration of clearance of the drug from the circulation. Additionally, $AUC_{glucose}$ was not calculated and was counted as missing if no plasma glucose at time 0 or at 30 minute during OGTT were obtained, or if glucose concentrations were not available for more than one OGTT time point. The changes in mean DBP in the subpopulation of patients who received spironolactone for the treatment of hypokalemia was analyzed separately and compared to the changes in DBP in patients who did not receive spironolactone. Efficacy analyses excluded those subjects who did not have any valid OGTT with $AUC_{glucose}$ measurement in C-DM group or did not have mean BP evaluated in C-HT group at baseline or after Day 1.

A responder analysis was used to measure a success on the each primary endpoint. A responder was defined as a subject who experienced at least a 25% reduction in $AUC_{glucose}$ from baseline to Week 24/ET (end of treatment visit) in C-DM cohort or ≥ 5 mmHg decline in mean DBP from baseline to Week 24/ET in C-HT cohort. The lower limit of the exact one-sided 95% binomial confidence interval for the responder rate was set at 20% to declare the primary efficacy measurement to be successful. The Sponsor stated that 20% was chosen as appropriate threshold to test against in this population because the spontaneous remission rate was expected to be close to 0. No adjustment in the analysis for the multiple comparisons was performed. The Sponsor stated that because of the enrollment of two or fewer subjects at each site the analysis of primary end-points by site was not performed.

For the purposes of the analysis all subjects were classified into the following populations:

- Safety population: all patients who received at least one dose of Korlym
- Efficacy populations:
- Intent-to-treat population (ITT): all patients who received at least one dose of Korlym (same as Safety population)
- Modified intent-to-treat population (mITT): all patients who received a total of at least 30 days of Korlym during the 24-week treatment period. The 30 days of treatment did not need to be consecutive. Patients who received ≥ 30 days of the study drug but discontinued Korlym prior to Week 24 were included in the mITT population.
- Completer population: all patients who completed the study through the Week 24 visit, were on study drug at the time of the Week 24 visit, and received at least 80% of the study medication doses (have been compliant with study medication).

The primary efficacy analysis was based on the mITT population. The analysis of the secondary, exploratory efficacy endpoints and safety analysis was based on ITT (Safety population) and mITT populations.

Medical Officer's comment:

1. *The Sponsor's choice of the 20% threshold to declare the success is acceptable: the spontaneous remission rate of Cushing's syndrome is very rare event in this population.*
2. *The Sponsor used a 95% one-sided binomial confidence interval with a lower bound of > 20% for analyzing the primary efficacy endpoints, however, the Division stated that that*

the FDA's standards for the assessing the efficacy is to use a two-sided alpha of 5% which corresponds to a two-sided 95% CI or 97.5% one sided CI (Review of SAP, May 10, 2010).Thus, biostatistician reviewer computed 2-sided 95% CI for each of the primary endpoints (refer to biostatistician review).

3. *The analysis of DBP in subgroup of patients who received and did not receive spironolactone for the treatment of hypokalemia is appropriate; spironolactone is antihypertensive drug and may affect BP value.*
4. *There were only few missing OGTT values that include single missing 60- or 90-min glucose values, and missing OGTT results at screening or Day 1 that were replaced by the OGTT results obtained at previous visits. Overall, these missing values do not impact the trial results.*

The secondary and exploratory efficacy and safety parameters were evaluated by descriptive statistics summarizing the data at baseline and the Week 24 visit. Three secondary endpoints: $AUC_{glucose}$ or decrease in antidiabetic medications, DBP or change in antihypertensive medications and key secondary endpoints were evaluated by responder analysis.
A responder was defined as:

- For $AUC_{glucose}$ change or change in antidiabetic medications endpoint:
  Subjects in C-DT group who, at the final visit as compared to the baseline visit, had reduction in $AUC_{glucose}$ by > 25% or was prescribed at least one fewer antidiabetic drug, or had a reduction in the total daily dose of any anti-diabetic drug
- For DBP change or change in antihypertensive medications endpoint:
  Subjects in C-HT and C-DM groups who, at the final visit as compared to the baseline visit, had a reduction In DBP by ≥ 5mmHg or were prescribed at least one fewer antihypertensive drug, or had a reduction in the total daily dose of any antihypertensive drug
- For key secondary endpoint:
  Subjects whose median reviewer score was +1 at any reviewed visit after baseline.
  The Sponsor chose the higher responder rate of 30% for the analysis of key secondary parameter than for the analysis of primary efficacy parameters (20%) or other secondary efficacy parameters (20%), because the assessments of change in clinical status by the DRB might result in more variability than that resulting from changes in the other efficacy variable. All other secondary efficacy parameters were evaluated as a percent change or change in absolute values from baseline as measured at the last visit.

AEs were coded accordingly to Medical Dictionary for Regulatory Activities (MedDRA 10.0).

No interim analysis was planned and performed.

Protocol Amendments
The original study protocol, dated November 27, 2007, was amended five times. All amendments were reviewed by this Medical Officer. Some of the relevant amendments are as follows:

1. On April 7, 2008:

- The baseline and 6-Week follow-up visits were changed to the unblinded visits for the DRB evaluation.

2. On August18, 2008:

- Initial dose of Korlym was changed (b) (4) to 300 mg, and the maximum dose was changed (b) (4) to 1200 mg. (b) (4) 1200 mg was allowed for the patients with severe Cushing's syndrome (but not above 20 mg/kg limit)
- Screening period was extended (b) (4) to 6 weeks to allow adjustment of the concomitant medications
- HbA_{1C} measurements were added at Day 1
- Inclusion and exclusion criteria were clarified: UFC had to be elevated on 2 collections within 4 months prior to the administration of the first dose of Korlym, systemic estrogens had to be stopped 6 weeks prior to Day 1 visit, anticoagulation medications were prohibited in women with intact uterus. Additionally, the restrictions on medications affected by CYP3A4 activity were clarified.

3. On February 17, 2009:

- CYP3A4 inducer carbamazepine and P-glycoprotein substrate colchicine were prohibited

4. On November 19, 2009:

- Evaluation of fasting lipid at 6-Week follow-up visit was added
- Endometrial biopsy requirements were added to the safety evaluation at screening and Week 24/ET visits. Endometrial biopsy was required at 6-Week follow-up visit if endometrial thickening persisted at that time
- Follow-up visit earlier than 6 Weeks was allowed

(b) (4)

- Sorafenib use was allowed and Fluvastatin use was prohibited during the study

5. On August 10, 2010:

- A Week 24/ ET visit was clarified as "end of study" visit.

Additional changes in the conduct of the pre-planned data analysis were implemented by the Sponsor, although the Sponsor did not specify whether these changes were included in protocol amendments:

- Amlodipine, hydrocodone, ibuprofen, omeprazole, rosuvastatin concentrations in blood were not measured
- If the data (weight, HbA_{1C}, $AUC_{glucose}$, DBP and SBP) did not meet assumptions necessary for the exploratory analysis (e.g., linearity, homogeneity of variance), either the raw data were log-transformed to meet the assumptions (population regressions on weight and $AUC_{glucose}$) or scatter plots analysis were substituted for the regression analysis (individual subject regressions on all five variables)
- Eplerenone was included in this analysis of the subjects taking spironolactone.
- Assessment of non-serious AEs was expanded to 14 days after end of treatment.
- Urinalysis summary and shift tables were deleted (data are listed only)
- Tables and listings summarizing medication reductions were deleted. Some other new tables were added and several planned tables were changed to Figures (the Sponsor did not specified what tables and figures were changed).

Results
The efficacy and safety results of the study will be further discussed in the Sections 6 (*Review of Efficacy*) and 7 (*Review of Safety*), respectively.

5.3.2 Study C1073-415 (Study 415)

Study Title:
An Open-label Extension Study of the Efficacy and Safety of Korlym in the Treatment of the Signs and Symptoms of Endogenous Cushing's Syndrome

Study Center(s) and Study Period:
Study was opened on July 21, 2009; study is ongoing.
Fourteen US centers participates in the study.
Data cutoff date is May 27, 2011.

Primary Objectives:
To evaluate the long term safety of Korlym in the treatment of the signs and symptoms of endogenous Cushing's syndrome

Design:
This is a Phase III, multicenter, open-label, extension study conducted in patients with endogenous Cushing's syndrome who completed Study 400 and received clinical benefit from Korlym in study 400.
The treatment schedule includes the following visits and periods:
1. Entry visit
The entry visit occurs within two weeks after completion of 6-week follow-up visit on the study 400. Korlym was not administered between these two visits.
2. Initial Period (6-month duration)
Initial period consists of 3 visits: at 1, 3 and 6 months.
3. 6-month continuation modules that can be added repetitively
Each continuation module consists of two visits (Visit A and Visit B) that occur at 3-month intervals. The modules were allowed to be added repetitively.
4. 6-week follow-up visit after the last visit on study drug.

The initial dose of Korlym in study 415 was the same dose that was administered during Week 24 visit in Study 400. Thus, initial dose of Korlym was individual for each subject. The dose was adjusted based on safety and/ or efficacy of the drug; the dose adjustment/ interruption algorithm was the same as in Study 400 (refer to Section 5.3.1).

Number of Subjects
A total of 50 patients were planned to be enrolled in the Study 415 based on the total number of subjects enrolled in the Study 400. Thirty four subjects completed 24-week treatment with

Korlym in study 400, of these, 30 subjects entered study 415 (cut-off date for the analysis May 27, 2011).

Patient Population:
Patients 18 years of age or older who had completed Week 24 and the 6-Week follow-up visits of study 400 and who, in opinion of the Investigator, were expected to maintain clinical benefit from Korlym were eligible to enter the study 415. Study 415 was an extension of study 400, thus the inclusion and exclusion criteria were identical to study 400 inclusion and exclusion criteria (refer to Section 5.3.1).

Endpoints:
Safety variables included an assessment of:
- adverse events
- clinical laboratory tests including hematology and urinalysis every 6 months, and serum chemistry at each study visit
- physical examination and vital signs at each study visit
- ECG at entry and end of study visits
- lipids values at entry and every 6 months thereafter. Evaluation of lipids was initiated after the approval of Amendment 2 (April, 2010)
- TSH and free T4 at entry and every 6 months thereafter. thyroid function tests (TFT) were repeated every 3 months in subjects who experienced an increase in TSH during Study 400
- ACTH, serum cortisol, and 24-hour UFC values (every 3 months)
- pituitary tumor size evaluated by MRI in subjects with Cushing's disease at entry and at the end of each continuation module. Subjects who had marked elevations in ACTH were allowed to have unscheduled MRI of pituitary
- endometrial thickness evaluated by transvaginal ultrasound at entry and every 3 months thereafter
- endometrial biopsies at entry visit and after first 12 months of treatment with Korlym or at early termination visit. Biopsies were initiated after approval of Amendment 2 (April, 2010). Additional endometrial biopsies are required in subjects with vaginal bleeding or increase endometrial thickness from study entry
- eye examination, including best corrected distance visual acuity, intra-occular pressure, dilated slit-lamp examination, dilated retinal examination, digital color fundus photography, autofluorescence imaging of the retina, digital fluorescein angiography, and spectral domain optical coherence tomography of the macula and nerve fiber layer at entry and every 6 months there after. Eye exams are initiated after approval of Amendment 3 (November, 2010)
- bone mineral density by DXA and measurements of bone metabolism markers every 6 month (after Amendment 4 approval in February, 2011).

Efficacy variables were exploratory in this study and included:
- Physician's Global Assessment of Disease severity every 3 months
- Subjects' Rated Disease Severity scores every 3 months

- Cushing's quality of life (QoL) assessment (after Amendment 3 in November, 2010).

  Medical Officer's comments:
  1. Ophthalmologic evaluation was initiated in November, 2010. Thus, no patient had baseline eye examination, and all patients have been on Korlym treatment at least for 6 months prior to the first eye examination.
  2. Results of QoL assessment are not presented in the abbreviated report, thus they will not be discussed in this review.
  3. Glycemic control including HbA_{1C} *or BP control were not evaluated in this study, thus, assessment of the long-term efficacy of the drug on the control of the signs and symptoms of Cushing's syndrome is complicated. Moreover, the "escape" phenomenon may occur in patients with Cushing's disease who are treated with Korlym chronically (Loriaux, 200; Nieman, 2002). This phenomenon is due to the reduced negative feedback by glucocorticoid receptor blockade, and may increase ACTH more. Elevated ACTH levels may stimulate further cortisol secretion. Eventually, very high cortisol levels may overcome glucocorticoid receptor blockade and lead to the loss of initial control of the disease. Thus, the evaluation of the long-term persistence of the efficacy of the drug would be desirable.*

Pharmacokinetics parameters included assessment of:

- Korlym, its metabolites and AAG serum levels prior to each injection of the study drug (trough levels) every 6 months.

Statistical Analyses

Safety data was analyzed by descriptive statistics. Summary statistics of serum chemistry, hematology, and urinalysis results were calculated for actual values and changes from baseline. Shift tables described the shift from the baseline values to the post-baseline visit values for serum chemistry, hematology, and lipid panel. Subjects who experienced hypokalemia (potassium $\leq$ 3.4 mEq/L) and who experienced severe hypokalemia (potassium < 2.5 mEq/L) during the study were analyzed separately. Vital signs, ECG, serum cortisol, 24-hour UFC, and ACTH were summarized by descriptive statistics. The adverse events were coded accordingly to MedDRA, version 10.0; the number and proportion of patients with at least one treatment-emergent AE (TEAE) were summarized by system organ class and preferred term. Bone mineral density parameters obtained in Study 415 were compared to the parameters obtained in the Study 400. Results of ophthalmological exams were summarized and reviewed by an independent expert.

For the purposes of the safety analysis all subjects were classified into the following populations, ITT and Safety populations. ITT and Safety populations were equivalent in this analysis and included all patients who received at least one dose of the study medication.

Assessment of efficacy was exploratory and based on ITT population. Physician's Global Assessment and Subject Rated Disease Severity scores were summarized at each visit by descriptive statistics. Scores obtained at post-baseline visits were compared to baseline scores using a paired t-test.

Interim analysis
Interim analysis of the safety data was conducted on September 15, 2010; the data from 20 subjects who were enrolled in the study was available at that time. The updated report dated August 10, 2011 was submitted later to the Agency. The data provided in the latest report are a cumulative summary providing all available up-to-date data on the 20 subjects included in the initial report and additional 10 subjects who entered the study since the last interim report.

Protocol Amendments
The original protocol, dated February 25, 2009 was amended four times. The relevant amendments were:
1. On May 8, 2009:
- Evaluation of lipids was added to the protocol.
- Treatment with fluvastatin, medication that has a large first pass metabolism mediated by cytochrome CYP3A4, was prohibited during the study to avoid drug-drug interaction
2. On April 27, 2010:
- Endometrial biopsies at entry and at 12 months and transvaginal ultrasound every 3 months were added to the study plan. The specialized lipid testing was added at selected sites
3. On November, 2010:
- Detailed eye examinations including retinal evaluation and Cushing's QoL questionnaire were added to the study plan
4. On February, 2011:
- The frequency of ECG assessments was increased to every 3 months
- DXA assessments for bone mineral density and evaluation of bone mineral markers at Month 6 visit and every 6 months thereafter were added to the protocol.

All other protocol amendments were reviewed by this Medical Officer and were found to be non relevant.

Results
Patient Disposition
Thirty of 34 subjects who completed 6-month treatment in Study 400 entered the study and had data available for the analysis (cut-off date for the analysis May 27, 2011). Of those, 27 subjects were still continuing the treatment as of August 10, 2011. All 30 subjects were analyzed for safety. Of these, 17 subjects were previously enrolled in C-DM cohort and 13 subjects - in C-HT cohort in Study 400. Eleven of 17 subjects who were enrolled previously in C-DM cohort, and 6/13 subjects who were enrolled previously in C-HT cohort were responders in Study 400, i.e. improved $AUC_{glucose}$ by > 25% or had decrease in DBP by ≥ 5mm Hg, respectively. Three of 30 subjects discontinued treatment prematurely: two subjects discontinued treatment because of AEs and one patient withdrew informed consent (# 24-001). The AEs that led to the study discontinuation were: death due to amyloidosis (subject # 06-003) and development of "multicystic endometrial echo complex" (subject #24-004). The following Table 9 shows the distribution of patients and reasons for the withdrawal from the study.

Table 9. Patients Disposition and Reasons for the Withdrawal in Study 415

	Total	C-DM*	C-HT*
Enrolled patients, n	30 (100%)	17	13
Total withdrawn, n	3 (10%)	2	1
Reasons for withdrawal:			
AE	2 (6.7%)	1	1
Consent withdrawn	1 (3.3%)	1	

*Cohorts that the subjects were enrolled in Study 400.

Prior and Concomitant Medication use

Concomitant medications were prescribed to all 30 patients during the study. Thirty seven percent of subjects were taking antidiabetic drugs, including 5 subjects who were receiving insulin formulations. Twenty-six of 30 patients (87%) were taking one or more antihypertensive drugs. Potassium supplements were taken by 20 patients (67%), spironolactone by 10 patients (33%).The most common medications (used by ≥ 25% of subjects) were analgesics (80% of patients), mineral supplements (73% of patients) and vitamins (66.7% of patients) , anti-inflammatory and antirheumatic drugs, diuretics and drugs for acid related disorders (60% of patients, each), renin-angiotensin system modulators and thyroid hormones (56.7% of patients, each), beta-blockers (46.7% of patients), lipid modifying agents and psychotropic drugs (43.3% of patients, each), antibacterial and psychoanaleptics (40% of patients, each), antithrombotic drugs (36.7% of patients), calcium channel blockers (33% of patients), anti-anemic products and sex hormones (26.7% of patients, each).

Medical Officer's comments:
Fewer patients in Study 415 were taking antidiabetic medications (37% of patients) as compared 65% of patients in Study 400 who was taking antidiabetic medications. This fact may be indicative of the persistent efficacy of Korlym in glycemic control over the time.

Safety results

The safety results of the study are discussed in Section 7. The exploratory efficacy variables and bone mineral density findings are discussed in Section 6.1.6.

5.3.3 Non-Cushing's Corcept-sponsored studies

All other Corcept-sponsored studies including PK studies in healthy volunteers and in special population, and in other indications provided supportive safety data only. The Studies 300, 301 and 425 were special safety studies evaluating effect of mifepristone on QT interval, HDL-cholesterol levels and development of rash; these studies are discussed in details in Section 7.4.5. All other studies are briefly summarized in Table 10 below and will not be discussed in details, unless otherwise specified. Of these studies, the study conducted in patients with Alzheimer's disease was the longest study- 300 mg of mifepristone was administered for 16 weeks. All other studies were single dose studies (PK studies) or studies of short duration (7-28 days).

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Table 10. Non-Cushing's Corcept's Studies That Provided the Supportive Safety Data for Mifepristone

Study	Objective(s) of the Study	Study design	Dosage regimen*	N of patients	Population studied	Total duration of Study	Efficacy Results
PK and Food effect Studies							
C1073-12	Compare PK and safety of SD of 600 mg mifepristone (MIFE) in a fed versus fasting state	Phase I, open label, randomized, 2-way crossover	Two SD 600 mg	50	Healthy volunteers 18-75 y.o	57 days	(b) (4)
C1073-20	Evaluate the effect of high-calorie, high-fat breakfast on PK of a single 1200-mg dose of KOR; evaluate effect of different doses of MIFE R on PK of MIFE and its metabolites	Phase I, open label, randomized	300, 600, 1200 mg; SD	24	Healthy volunteers, 18-65 y.o Groups: 24 (fast, 1200 mg) 22 (fed, 1200 mg) 10 (fast, 600 mg) 10 (fast, 300 mg)	69 days	
C1073-22	Evaluate the effect of formulation differences on PK of mifepristone following a single 300 mg dose	Phase I, open label, randomized, 3-way crossover	Three SD 300 mg (tablets from different mfg. lots)	15	Healthy male volunteers, 18-65 y.o	10 weeks	
C1073-27	Evaluate the food effect (34% fat) on PK of MIFE and its metabolites	Phase I, open label, randomized, 2-period crossover	1200 mg x 15 days (fast x 7 days, fed x 8 days)	24	Healthy volunteers, 18-65 y.o	12 weeks	

							(b) (4)
PK Study in Special Population							
C1073-05	Evaluate safety and PK of SD and MD of C- 1073 (mifepristone) in hepatically-impaired subjects (Child-Pugh B) as compared to healthy volunteers	Phase I, open label, 2-period	600 mg X 1 day; 600 mg X7 days	20	With hepatic impairment (10) and healthy (10), 18-79 y.o	3 months	
C1073-19	Evaluate the effect of renal impairment on PK of MIFE and its metabolites following MD of MIFE administration	Phase I, open label two-stage	1200 mg X 7 days	18	With severe renal impairment (GFR <30 mL/min/1.73 m^2 but not on dialysis) (10) Healthy volunteers (8) 18-79 y.o	8 -11 weeks	
DDI studies							
C1073-	Evaluate the effect of	Phase I,	MIFE *:	20	Healthy	9 weeks	

16	mifepristone on PK of a Single Oral Dose of fluvastatin (FLU) a CYP2C9 probe	open label, fixed sequence	1200 mg x 7 days FLU: 40 mg , two SD		volunteers	
C1073-23	Evaluate the effect of SD and MD of MIFE on PK of digoxin (DIG) at steady state	Phase I, open label, fixed sequence, three-treatment	MIFE : 1200 mg x 10 days DIG: 0.25 mg x 1 day, than 0.125 mg x 17 days (KOR+DIG x 7 days)	24	Healthy volunteers, 18-65 y.o	39 days
C1073-24	Evaluate the effect of SD and MD of MIFE on PK of alprazolam (ALP), a CYP3A4 substrate	Phase I, open label, fixed sequence, 3-period crossover	MIFE : 1200 mg x13 days; ALP: 1mg , three SD (alone, with SD of MIFE and at the end of 13 days treatment with MIFE)	16	Healthy volunteers, 18-65 y.o	10 weeks
C1073-25	Evaluate the effect of SD and MD of MIFE on PK of simavastatin (SIM)	Phase I, open label, fixed sequence, 2-period, tree-	MIFE: 1200 mg x 10 days SIM: 40 mg , three SD	20	Healthy volunteers, 18-65 y.o	39 days

(b) (4)

		treatment crossover	(alone, with SD of MIFE and at the end of 10 days treatment with MIFE)			
C1073-26	Evaluate the effect of SD and MD of cimetidine (CIM) on SD and MD PK of MIFE and of SD and MD of MIFE on SD and MD PK of CIM	Phase I, open label, fixed sequence, 3-period, 6-treatment crossover	MIFE: 300 mg x 14 days CIM: 800 mg x 35 days	22	Healthy volunteers, 18-65 y.o	11 weeks
Studies in other indications: Major Depressive Disorder (MDD) with Psychotic Features						
C1073-99-01	Safety and efficacy of three dosing regimens of MIFE	Phase II, multicenter, open-label, dose-ranging, parallel group	50 mg x 7 days 600 mg x 7 days 1200 mg x 7 days	33	Adult patients with MDD with psychotic features	UN^
C1073-02	Safety and efficacy	Phase III, multicenter, randomized, double-blind, placebo-	600 mg x 7 days Placebo x 7 days	208	Adult patients with MDD with psychotic features who were treated	56 days

(b) (4)

							(b) (4)
		control			previously with antidepressant medications, 18-75 y.o		
C1073-03	Safety and efficacy	Phase III, randomized, double-blind placebo-control	600 mg x 7 days	221	Adult patients with MDD with psychotic features who are not receiving antidepressant medications, 18-75 y.o	56 days	
C1073-04	Evaluate efficacy of MIFE in patients who previously demonstrated a rapid response (improvement in psychotic symptoms) to treatment with either MIFE or placebo in Studies C-1073-02 or C-1073-03	Phase III, multicenter, open-label	600 mg x 7 days	28	Patients with MDD with psychotic features who previously demonstrated a rapid response to MIFE or placebo in studies C-1073-02 or C-1073-03 and participated in those studies for at least 12 weeks.	28 days	
C1073-06	Safety and efficacy of 3 different doses of MIFE plus antidepressants	Phase III, randomized, double-blind	300 mg x 7 days 600 mg x7	443	Patients with MDD with psychotic	56 days	

		placebo-controlled, parallel group	days 1200 mg x7 days Placebo x7 days combined with antidepressant x 56 days		features		
C1073-07	Safety and efficacy	Phase III, multicenter, randomized, double-blind placebo-control	600 mg x 7 days Placebo x 7 days	258	Patients with MDD with psychotic features	56 days	
C1073-09	Safety and efficacy	Phase III, multicenter, randomized, double-blind, placebo-control	600 mg x 7 days Placebo x 7 days	247	Patients with MDD with psychotic features	56 days	
C1073-10	Efficacy and safety of MIFE in patients with MDD who previously received one course of therapy with either MIFE or placebo	Phase III, open-label, extension study	600 mg x 7 days, the treatment were repeated in 28-day cycles based on the psychiatric	87	Patients with MDD with psychotic features who completed studies C1073-07 or C1073-06 and did not require immediate	56 days	

(b) (4)

			and safety assessment of the patient		intervention with an antipsychotic or electroconvulsive therapy treatment (ECT)	
C1073-13	Efficacy and safety of MIFE in patients with MDD who previously received one course of therapy with either KOR or placebo	Phase III, multicenter, open-label, extension study	600 mg x 7 days, the treatment were repeated in 28-day cycles based on the psychiatric and safety assessment of the patient	104	Patients with MDD with psychotic features who completed Study C1073-09 and did not require immediate intervention with an antipsychotic or ECT	56 days
Studies in other indications: Alzheimer's disease						
C1073-71	Safety and efficacy of 300 mg of MIFE on cognition and behavior of Alzheimer's patients	Phase II, multicenter, randomized, double-blind placebo-control	300 mg x 16 weeks Placebo x 16 weeks	81	Patients with Alzheimer's disease	20 weeks
Studies in other indications: prevention of weight gain						
C1073-200	Efficacy and safety of MIFE in the prevention of olanzapine (OLA)-induced weight gain	Phase II, randomized, double-blind, placebo-control	MIFE 600 mg plus OLA 5-10 mg x 3 weeks or Placebo 600	15	Healthy males, 18-40 y.o	7 weeks

(b) (4)

			mg plus OLA 5-10 mg x 3 weeks			
C1073-200-I	Efficacy and safety of MIF in the prevention of OLA-induced weight gain	Phase II, randomized, double-blind placebo	MIFE 600 mg x plus OLA 2.5-7.5 mg x 2 weeks or Placebo 600 mg plus OLA 2.5-7.5 mg x 2 weeks	59	Healthy males, 18 - 40 y.o with baseline BMI 18-25 kg/m2	6 weeks
C1073-205	Efficacy and safety of MIFE in the prevention of risperidone (RIS)-induced weight gain	Phase II, randomized, double-blind placebo	MIFE 600 mg plus RIS 0.5 -2 mg x 28 days or Placebo 600 mg plus RIS 0.5 -2 mg x 28 days	76	Healthy males, 18-40 y.o with baseline BMI 18-23 kg/m2	56 days

(b) (4)

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication for Korlym is treatment of clinical and metabolic effects of hypercortisolemia in patients with endogenous Cushing's syndrome, including:

- patients with Cushing's disease who have not adequately responded or relapsed after surgery
- patients with Cushing's disease who are not candidates for surgery

(b) (4)

6.1.1 Methods

The efficacy of Korlym in the treatment of patients with endogenous Cushing's syndrome is examined in a single pivotal Study 400. The incidence of Cushing's syndrome is very low in general population, and approved medical treatment of hypercortisolemia is not available. Therefore, as was discussed and agreed during the review of the original IND # 76480 for Korlym (August 23, 2007) and in the correspondence dated September 6, 2007 between the Sponsor and Agency, the use of a single study appropriately designed and of sufficient duration will be sufficient for this NDA approval. Study 400 is discussed in details Section 5.3.1.Briefly, this was a 24-week duration, open-label, non-comparative, multicenter clinical study involving 50 subjects with endogenous Cushing's syndrome who had IGT/ DM or hypertension induced by hypercortisolemia.

Additional supportive evidence for the efficacy of KOR in patients with Cushing's syndrome are obtained from the published reports of the use of mifepristone in patients with CS submitted by the Sponsor in this NDA; these literature reports are reviewed in sections 6.1.10, 7.7.2 and 9.1. The Sponsor emphasized that the efficacy data obtained from the literature provide supportive evidences only for the efficacy of Korlym in patients with Cushing's syndrome and will not be inserted in the label.

6.1.2 Demographics

Fifty patients with Cushing's syndrome, mean age 45 years, were included in the Safety (and ITT) population; 35 of these patients were females (70%). Twenty-nine of fifty patients were enrolled in C-DM cohort and 21/50 patients were enrolled in C-HT cohort. No meaningful difference in baseline demographic characteristics between cohorts in the ITT population was seen (Table 11). The mean age of patients in C-DM cohort was 44 years; the mean age of patients in C-HT cohort was 46 years. More females than males were enrolled in both cohorts: 22/29 (75.9%) females in C-DM cohort and 13/21 (61.9%) females in C-HT cohort. Most of the

patients in ITT population were obese (BMI 35.7 kg/m2); obesity is common finding in patients with hypercortisolemia.

Table 11. Demographics and Body Measurements at Baseline (ITT/Safety Population)

Characteristics	C-DM* (n=29)	C-HT^ (n=21)	Total (n=50)
Sex, n (%)			
Female	22 (75.9)	13 (61.9)	35 (70)
Male	7 (24.1)	8 (38.1)	15 (30)
Age, yrs			
Mean (CD)	44.4 (13.7)	46.7 (8.83)	45.4 (11.85)
Median	41	46	45
Range	26-71	26-67	26-71
Weight, kg			
Mean (CD)	105 (33.54)	91.4 (21.10)	99.5 (29.55)
Median	102	88.2	92.4
Range	61.3- 198.7	62.7-150.5	61.3-198.7
BMI, kg/m^2			
Mean (CD)	37.4 (11.2)	33.4 (7.44)	35.7 (9.9)
Median	35.1	31.8	33.5
Range	24-66.4	24.5-53.6	24.1-66.4
Waist circumference, cm			
Mean (CD)	124 (21.7)	11 1 (15.8)	119 (20.3)
Median	120	104	115
Range	97.9 -178.4	88.5-153.5	88.5-178.4

Source: Sponsor's table 8, Module 5, Vol 31, p. 64;
*C-DM cohort included patients with impaired glucose tolerance/Dm; ^C-HT cohort included patients with hypertension but without impaired glucose tolerance/DM.

Medical Officer's comments:
In general population, Cushing's disease occurs most frequently in middle age patients and affects women four times more frequently than men (Newell-Price et al, 2006). Thus, considering that the majority of the patients enrolled in this study were diagnosed with Cushing's disease, the demographic characteristics of studied population matches the demographic characteristics of patients with Cushing's syndrome in general population.

Cushing's syndrome characteristics at baseline:

1. Cushing's syndrome etiology:
   - Majority of patients were diagnosed with Cushing's disease: 43/50 (86%) patients (24 patients in C-DM, 19 patients in C-HT)
   - 42 patients had pituitary surgery in past; one patient was not candidate for surgery (C-DM)
   - 18/ 43 patients (43%) received prior radiotherapy: 12 patients in C-DM, 6 patients in C-HT). The mean time interval since the last radiation treatment was 31.5 ± 24 months (range 25 days-7.2 years).
   - 3/ 50 (6%) patients had adrenal cancer (2 patients in C-DM, 1 patient in C-HT).
   - 4/50 (8%) patients had ectopic ACTH-secreting tumors (3 patients in C-DM, 1 patient in C-HT).

2. Prior medical treatment of hypercortisolemia:

- All patients were naïve to mifepristone therapy.
- Other antiglucocorticoid therapy (Table 12):
- 18/50 (36%) patients were naïve to the other antiglucocorticoid therapy
- 23/50 (46%) patients were treated previously with one or more antiglucocorticoid drug
- No information about previous medical treatment in 9 patients was available

Total of 23 patients were treated previously with 1 or more antiglucocorticoid medications for 1-84 months (mean 17 months). The majority of patients were treated with ketoconazole, 5 patients were treated with more than 1 drug. All treatments were discontinued > 1 month prior to the study entry, except for mitotane treatment: three subjects with adrenal cancer continued treatment with mitotane during the study. One patient (#10-001) with ACTH- and gastrin-producing pancreatic tumor was on Octreotide for 6 months prior to the study entry and continued treatment with octreotide during Study 400 and Study 415. Thirteen of 23 (56%) patients failed medical treatment.

Table 12. Medical Therapy of Hypercortisolemia (ITT/Safety Population)

Drugs	Total number of patients (n)	Results, n (duration of treatment, month)		
		Failed	Respond	Unknown
Ketoconazole	20	12 (3-84)	2** (4-11)	6 (1-14)
Metyrapone	1	1(1)		
Mitotane	3			3*
Octreotide	2	1** (5)		1 *** (12)
Cabergoline	2	1 (9)		1*** (12)

*3 patients were treated with mitotane after ketoconazole was discontinued; mitotane was continued during the study.
** 1 patient had partial response, but ketoconazole was discontinued due to the interaction with the other meds.
** Octreotide was continued during the study.
*** Patient was treated with octreotide and cabergoline simultaneously; treatment was discontinued due to the lack of insurance.

3. Signs and symptoms of hypercortisolemia at screening (Table 13):
All patients had two or more typical Cushing's syndrome features at screening including Cushingoid appearance, hirsutism, striae, increased body weight, proximal muscle weakness, osteopenia and psychiatric symptoms. The most typical features of Cushing's syndrome (Nieman et al, 2008), Cushingoid appearance and increased weight, were present in 49/51 patients. Cushingoid appearance was absent in one patient in C-HT cohort; this patient had increased weight, psychiatric symptoms and hirsutism, and had non-suppressible low dose dexamethasone suppression test (LDDST) and elevated UFC levels. One patient in C-DM cohort had normal weight at screening, but had all other common features of Cushing's syndrome. Both patient also had pituitary adenoma and failed pituitary surgery in past; both patients had confirmation of ACTH-producing pituitary tumor by pathology staining.

Table 13. Cushing's Syndrome History and Signs/Symptoms at Screening (Safety Population)

Characteristic	C-DM (N=29) n (%)	C-HT (N=21) n (%)	Overall (N=50) n (%)
Cushing's etiology/syndrome history			
Cushing's disease	24 (82.8)	19 (90.5)	43 (86.0)
Ectopic (ACTH)	3 (10.3)	1 (4.8)	4 (8.0)
Adrenal carcinoma	2 (6.9)	1 (4.8)	3 (6.0)
Cushing's disease that			
Recurred after primary pituitary surgery	12 (41.4)	9 (42.9)	21 (42.0)
Persisted despite pituitary surgery (failed pituitary surgery)	16 (55.2)	14 (66.7)	30 (60.0)
Had been treated with radiation therapy to the pituitary	12 (41.4)	6 (28.6)	18 (36.0)
Was not treatable with surgery	5 (17.2)	1 (4.8)	6 (12.0)
Existed in subjects who were not candidates for surgery*	5 (17.2)	1 (4.8)	6 (12.0)
Subjects with diabetes mellitus or impaired glucose tolerance at screening, n (%) **	29 (100.0)	0 (0.0)	29 (58.0)
Subjects with hypertension at screening, n (%)	22 (75.9))	21 (100.0)	43 (86.0)
Signs and symptoms related to hypercortisolemia, n (%)			
Cushingoid appearance	29 (100.0)	20 (95.2)	49 (98.0)
Hirsutism and/or violaceous striae or acne	19 (65.5)	11 (52.4)	30 (60.0)
Increased body weight or central obesity	29 (100.0)	20 # (95.2)	49 (98.0)
Proximal muscle weakness	15 (51.7)	12 (57.1)	27 (54.0)
Low bone mass (DXA T-score < -1.0)	3 (10.3)	10 (47.6)	13 (26.0)
Psychiatric symptoms (depression or psychosis)	17 (58.6)	9 (42.9)	26 (52.0)

Source: Sponsor's table 9, Module 5, Vol 31, CSR 400

* One subject had *de novo* Cushing's disease but was not a candidate for surgery (#24-005). Other subjects who had Cushing's disease that "was not treatable with surgery" or "existed in subjects who were not candidates for surgery" had previously undergone pituitary surgery.

** Three subjects in the C-HT group (# 07-006, 07-007, and 24-002) entered with a diagnosis of diabetes; they were not enrolled in C-DM cohort because did not have confirmation of DM by two abnormal OGTTs.

4. Baseline biochemical features of Cushing's syndrome:

- Majority of patient had elevated UFC levels at baseline (normal range is < 42.4 mcg/24 hrs): mean values were 365 ± 1049 mcg/24 hr, median values were 100 mcg/24 hr, range 21.4-7152 mcg/24 hr.
- ACTH was elevated in majority of patients with Cushing's disease and ectopic ACTH-producing tumors. ACTH levels were higher in patients with ectopic Cushing's syndrome compared to ACTH levels in patients with pituitary tumors (152 ± 140 pg/ml (median 118 pg/ml, range 30-345 pg/ml vs. 62.7 ± 51 pg/ml (median -50 pg/ml, range- 7-241 pg/ml), respectively). All patients with adrenal cancer had elevated UFC levels and undetectable ACTH levels.

Medical Officer's comments:

1. *The detailed information about the previous medical treatment of hypercortisolemia and previous radiotherapy in patients with Cushing's disease was not provided in the original NDA. In 74-day filling letter the Division asked the Sponsor to provide information about previous medical treatment of hypercortisolemia in patients with Cushing's syndrome (June 28, 2011). The Sponsor submitted the following requested information on July 13, 2011:*
   - *The Sponsor indicated that an accounting for previous medical treatments of hypercortisolemia was not required by protocol. Thus, the information regarding previous medical treatment of hypercortisolemia was obtained post-hoc using an expanded medical history questionnaire and by correspondence with Investigators and the provided data may underestimate the true numbers. The Sponsor also stated that washout period of at least one month was required for those who were treated with antiglucocorticoid medications in past. The washout period of one month is acceptable, and carryover effect is not expected.*
   - *Radiotherapy to pituitary has a delayed onset of beneficial effects, thus there was a concern that the improvement in patients' signs and symptoms of Cushing's syndrome might be due to the delayed onset of action of radiotherapy and not to the Korlym itself. Thus, this reviewer analyzed the UFC and ACTH levels at each study visit and at final visit in all patients who received prior radiation to the pituitary. The effective radiation treatment should lower the ACTH and cortisol levels; in contrast, Korlym does not lower ACTH or cortisol levels. Seventeen of 18 patients treated with radiation to pituitary in the past had elevated UFC and ACTH levels <u>at the end of the study,</u> indicating the lack of the overall efficacy of radiation therapy. Only one patient in C-HT cohort who had radiation therapy 7 years ago had normal UFC levels, but elevated ACTH level at the follow-up visit. In conclusion, most likely radiation therapy was ineffective in these patients, and observed improvement in the signs and symptoms of hypercortisolemia was due to the effect of Korlym.*
2. *All enrolled patients had elevated UFC levels above normal range, this was consistent with inclusion criteria. Few patients with Cushing's disease had UFC elevated to less than 4 folds above upper normal limit at baseline; mildly elevated UFC may be seen in patients with pseudo-Cushing's (Nieman, 2010). In this reviewer opinion, patients enrolled in the study had very high probability of having Cushing's syndrome (all patients had failed pituitary surgery in past and had documentation of ACTH immunoreactivity on a pathological evaluation of pituitary tissue), thus even mildly elevated UFC levels are diagnostic of Cushing's syndrome in these patient population.*
3. *Few patients had fluctuation in UFC levels from high to normal during the study, thus, thee was a concern of enrolling patients with cyclic disease. Cyclic Cushing's syndrome occurs in up to 20% in patients with Cushing's syndrome (Alexandraki et al, 2009); patients with cyclic CS might have improvement in hypercortisolemia symptoms because of the decreased ACTH and cortisol levels and not because of the treatment itself. Thus, the ACTH and UFC levels at each study visit, particularly in*

those patients with diabetes who were considered responders at the end of the study, were further analyzed by this reviewer:

- *No consistent pattern in decreasing ACTH and UFC levels throughout the study was noted; the decreased UFC levels were associated with elevated ACTH levels, thus the significance of occasionally decreased UFC levels is unknown. Moreover, all but one patient in the group of C-DM responders had elevated ACTH and UFC levels at the time of the primary endpoint evaluation (Week 24 visit). One patient (#017002) had low UFC and ACTH levels at final visit, but elevated UFC and ACTH levels during all previous visits, thus, the single low values can not be interpreted. Therefore, in this reviewer opinion, no improvement in symptoms of hypercortisolemia including glucose and BP control was secondary to the cyclic production of cortisol.*

Treatment compliance

Compliance with the study drug was determined by the review of subject's drug diary and of the drug accountability log in the clinic. The compliance with the study drug was higher in subjects in diabetes cohort. This difference might be due to the small and imbalanced number of patients enrolled in each cohort. Table 14 below summarizes the number of subjects with > 80% drug compliance.

Table 14. Summary of Subjects with > 80% Compliance with Study Drug by Analysis Population and Cohort

Analysis Population	**Cohort**	
	C-DM n/N (%)	**C-HT n/N (%)**
mITT	23/25 (92.0)	15/21 (71.4)
ITT	24/29 (82.8)	15/21 (71.4)
Completer	20/20 (100.0)	13/13 (100.0)

Source: Sponsor's table 12, ,Module 5, Vol 31, CSR 400, p. 69

Prior and Concomitant medications

All 50 subjects received at least one concomitant medication during the study. The most common medications (used by ≥ 20% of subjects) are summarized in Table 15.

Table 15. Concomitant Medications Used by ≥ 20% or More of the Overall Study Population (ITT/Safety Population)

Medication Class	C-DM (N=29) n (%)	C-HT (N=21) n (%)	Total (N=50) n (%)
Number of subjects with at least one concomitant medication	29 (100.0)	21 (100.0)	50 (100.0)
Mineral supplements	21 (72.4)	15 (71.4)	36 (72.0)
Vitamins	18 (62.1)	15 (71.4)	33 (66.0)
Analgesics	19 (65.5)	14 (66.7)	33 (66.0)
Diuretics	20 (69.0)	10 (47.6)	30 (60.0)
Agents acting on the renin-angiotensin system	17 (58.6)	13 (61.9)	30 (60.0)
Antibacterial for systemic use	15 (51.7)	8 (38.1)	23 (46.0)
Drugs for acid related disorders	13 (44.8)	10 (47.6)	23 (46.0)
Psycholeptics	12 (41.4)	10 (47.6)	22 (44.0)
Beta blocking agents	14 (48.3)	7 (33.3)	21 (42.0)
Psychoanaleptics	12 (41.4)	9 (42.9)	21 (42.0)
Anti-inflammatory and antirheumatic products	8 (27.6)	12 (57.1)	20 (40.0)
Drugs used in diabetes	19 (65.5)	1 (4.8)	20 (40.0)
Thyroid therapy	9 (31.0)	10 (47.6)	19 (38.0)
Lipid modifying agents	13 (44.8)	3 (14.3)	16 (32.0)
Calcium channel blockers	11 (37.9)	6 (28.6)	17 (34.0)
Corticosteroids for systemic use	9 (31.0)	7 (33.3)	16 (32.0)
Antithrombotic agents	8 (27.6)	6 (28.6)	14 (28.0)
Sex hormones and modulators of the genital system	8 (27.6)	6 (28.6)	14 (28.0)
Antiemetic and antinauseants	7 (24.1)	5 (23.8)	12 (24.0)
Intestinal antiinflammatory /antiinfectious agents	5 (17.2)	5 (23.8)	10 (20.0)
Blood substitutes and perfusion solutions	5 (17.2)	5 (23.8)	10 (20.0)
Drugs for treatment of bone diseases	4 (13.8)	6 (28.6)	10 (20.0)

Source: Sponsor's table 10, p. 66, Module 5, Vol 31, CSR 400
The concomitant medications of the particular interest are highlighted.

Total of 20/50 patients (40%) were on antiglycemic drugs: 19/29 patients (65.5%) of patients in C-DM cohort and 1 patient in C-HT cohort (this patient was not enrolled in the C-DM cohort because he did not have two baseline OGTT evaluations). The most common antidiabetic medication was insulin (12 subjects); other antidiabetic medications included exenatide, sulfonylureas, metformin, Janumet (metformin and sitagliptin) and Sitagliptin (Table 16).

Table 16. Concomitant Medications Used to Treat Diabetes (ITT/Safety Population)

Medication	C-DM (N=29)	C-HT (N=21)	Overall (N=50)
Exenatide	2		2
Glibenclamide	1		1
Glimepiride	2		2
Glipizide	2		2
Insulin aspart	5	1	6
Insulin detemir	2		2
Insulin glargine	9		9
Insulin glulisine	1		1
Insulin human	2	1	3
Insulin injection, isophane	1	1	
Insulin lispro	3	3	
Insulin novolin 70/30	1		1
Metformin	10		10
Janumet (metformin and sitagliptin)	2		2
Sitagliptin	3		3

Source: Sponsor's table 11, p. 68, Module 5, Vol 31, CSR 400.

Majority of subjects were taking more than one antihypertensive medication. The beta-blockers, agents acting on rennin-angiotensin system and calcium channel blockers (21/50 (42%), 30/50 (60%) and 17/50 (34%) of patients, respectively). Additionally, 30/50 subjects (60%) (20 subjects in C-DM cohort and 10 subjects in C-HT cohort) took diuretics for hypertension treatment. Four patients in C-DM cohort received spironolactone; the use of spironolactone was prohibited for the BP control, but was allowed for the potassium control. The antihypertensive medications are summarized in Table 17.

Table 17. Concomitant Medications Used to Treat Hypertension (ITT/Safety Population)

Medication	C-DM (N=29)	C-HT (N=21)	Total (N=50)
Agents acting on the renin-angiotensin system			
Aliskiren		1	1
Amlodipine with valsartan		1	1
Benazepril		1	1
Co-diovan	2		2
Enalapril (enalapril and enalapril maleate)		2	2
Hyzaar		1	1
Irbesartan	2	1	3
Lisinopril	7	6	13
Losartan potassium	2		2
Olmesartan medoxomil	1	2	3
Prinzide		2	2
Pritor	1		1
Ramipril	1		1
Valsartan	3		3
Antihypertensives			
Clonidine	3	2	5
Hydralazine	1		1
Beta blocking agents			
Atenolol	4	3	7
Carvedilol	2		2
Labetalol	1		1
Metoprolol	3	4	7
Nebivolol	4		4
Calcium channel blockers			
Amlodipine	4	5	9
Diltiazem	2		2
Nifedipine	2	2	4
Verapamil	1		1
Diuretics			
Dyazide		1	1
Furosemide	5		5
Hydrochlorothiazide	3	2	5
Spironolactone	4	4	

Source: Sponsor's table 11, p. 68, module 5, Vol 31, CSR 400

6.1.3 Subject Disposition

Eighty-four patients were screened; 34 patients were not enrolled (the reason for the lack of eligibility is not provided by the Sponsor). A total of 50 patients were planned and enrolled in the trial. Twenty-nine subjects were enrolled in the cohort of subjects with diabetes mellitus (DM) and/or impaired glucose tolerance (C-DM) and 21 subjects were enrolled in the cohort of subjects with hypertension (C-HT) but without DM. Fifty subjects received at least one dose of

study drug (ITT and Safety populations); 34 subjects (68%) completed the study. Forty-six patients received at least 30 days of Korlym (not needed to be consecutive) during the study period and were included in the mITT population. Four subjects in C-DM cohort were excluded from mITT population; three subjects withdrew informed consent (# 15-001, #15-005, #20-002) and one subject (# 24-005) died.

The following Table 18 shows the distribution of the patients in the analysis populations. Thirty-three subjects comprised completer population; sixteen subjects (9-in C-DM cohort and 7-in C-HT) cohort were withdrawn prematurely from the study and one subject # 07-010 (C-HT) was not enrolled in the completer cohort for unspecified reason. The reasons for the premature withdrawal of 16 subjects from the study were:

- Seven patients were withdrawn due to AEs: 2 patients in C-DM cohort (#07-003, #08-003) and 5 patients in C-HT (#01-001, #07-007, #07-009, #08-014, #22-003); 3/5 patients in C-HT were withdrawn due to SAEs
- Two patients died: # 07-006 (C-HT) and #20-002(C-DM)
- Five subjects withdrew informed consent (4-in C-DM cohort and 1- in C-HT cohort)
- One subject with adrenal cancer (# 07-008) was "too ill to travel"
- One subject was withdrawn due to severe non-compliance with study procedures (# 08-013).

Overall, 34 subjects completed 24-week treatment period and 40 subjects (80%) attended 6-Week follow up visit (22-in C-DM cohort and 18-in C-HT cohort): additional 6 subjects who terminated study early returned for follow up visit.

Table 18. Patient Disposition by Populations and Study Cohort (n (%))

Population	**Treatment group**		
	C-DM	**C-HT**	**Total**
ITT and Safety population (n=50)	**29(58%)**	**21 (42%)**	**50 (100%)**
Completer population (n=33)	**20**	**13**	**33 (66)**
Total excluded	9	7	17
Reason for exclusion			
AE	2^	5^^	7
Death	1[#]	1[##]	2
Consent withdrawn by subject	4	1	5
Other	2*	1**	3
mITT population (n=46)	**25**	**21**	**46 (96%)**
Total excluded	4		4
Reason for exclusion			
Death	1		1
Consent withdrawn by subject	3		3

^Subjects' last doses of Korlym were 300 and 1200 mg; they were withdrawn in 39 and 69 days after treatment initiation, respectively.
^^ The last doses of Korlym was 300 mg in 3 subjects, 600 mg and 1200 mg in one subject each; subjects were withdrawn from the study in 60, 111, 114, 34, and 84 days after treatment initiation, respectively.
[#] Subject #20-002 was on 300 mg of Korlym and died on Day 14 of the study.
[##]Subject # 07-006 was one 1200 mg of Korlym and died in 112 days after treatment initiation.
*Subject #07-008 was withdrawn because she was too ill to travel and Subject #08-013 was withdrawn due to the study non-compliance; **Subject #07-010 was excluded form the completer population for unspecified reason.

6.1.4 Analysis of Primary Endpoint(s)

Because the pharmacodynamics effect of Korlym does not result in decreased cortisol levels, it was not possible to use cortisol levels as an efficacy endpoint in the trial. Therefore, the signs and symptoms of endogenous Cushing's syndrome were assessed. Blood glucose and blood pressure measurements were chosen as a two primary end-points because they are quantitative measures of two main manifestations of Cushing's syndrome-hypertension and impaired glucose tolerance. Moreover, the causes of death in Cushing's syndrome are mainly due to cardiovascular complications and the risk of death is independently increased with co-existing diabetes mellitus and/or hypertension (Clayton et al, 2011). Thus, control of BP and glucose in patients with Cushing's syndrome may decrease overall high morbidity and mortality associated with hypercortisolemia and are relevant endpoints.

To evaluate glucose control in subjects with DM or impaired glucose tolerance the change in $AUC_{glucose}$ during the OGTT from baseline to Week 24 was chosen as primary efficacy variable. To evaluate BP control in subjects with hypertension the change in diastolic blood pressure from baseline to Week 24. A responder analysis was used to measure the success. A responder was defined as a subject who experienced ≥ 25% decrease in $AUC_{glucose}$ (C-DM cohort) or ≥ 5 mm decrease in DBP (C-HT cohort) from baseline to Week 24. Each primary measurement was considered to be positive or successful if the lower limit of the exact 95% binomial CI for the responder rate was ≥ 20%. The primary analysis is based on mITT population, unless specified otherwise. The statistical analysis of primary endpoints is discussed in Section 5.3.1.

Medical Officer's comments:
The limitations of the chosen primary endpoints are:

- *$AUC_{glucose}$ may be affected by multiple factors including diet, exercise, and stress and has day-to-day variability.*
- HbA_{1C} *has less day-to-day variability is not* affected by the above factors *and a standard measure of long-term glycemic control. The current ADA recommendations are to perform HbA_{1C} testing routinely in all patients with diabetes as part of continuing care. Moreover, HbA_{1C}, as a measure of glycemic control, is the FDA-recommended efficacy endpoint for approval of anti-diabetic therapies. Thus, the evaluation of HbA_{1C} would be a more relevant efficacy endpoint in patients with diabetes, although the change in HbA_{1C} is of less clinical significance in patients with impaired glucose tolerance but without diabetes. The HbA_{1C} levels remain within normal range in patients with IGT. Control of HbA_{1C} by the study drug was the secondary endpoints in both studies. Overall, $AUC_{glucose}$ changes supported by HbA_{1C} changes reliably evaluate the overall glycemic control in these patients.*
- *A few patients were enrolled in the C-HT cohort based on elevated SBP values while having normal DBP (inclusion criteria were elevated DBP and/or SBP). For these patients the improvement in already normal DBP values is of unknown clinical significance; as per current recommendations of Joint National Committee (JNC) on Prevention, Detection, Evaluation and Treatment of High BP (The Seventh report on the JNC, 2004), patients with SBP < 140 mm Hg or DBP <90 mm Hg are not candidates for the drug therapy. Moreover, the improvement in DBP without controlling SBP does not decrease risk of cardiovascular*

morbidity and mortality and these patients still carry the diagnosis of hypertension. Thus more relevant endpoint would be control and normalization of both SBP and DBP during the study.

Primary Efficacy Outcome in C-DM cohort: change in $AUC_{glucose}$ at Week 24/ET from baseline during OGTT

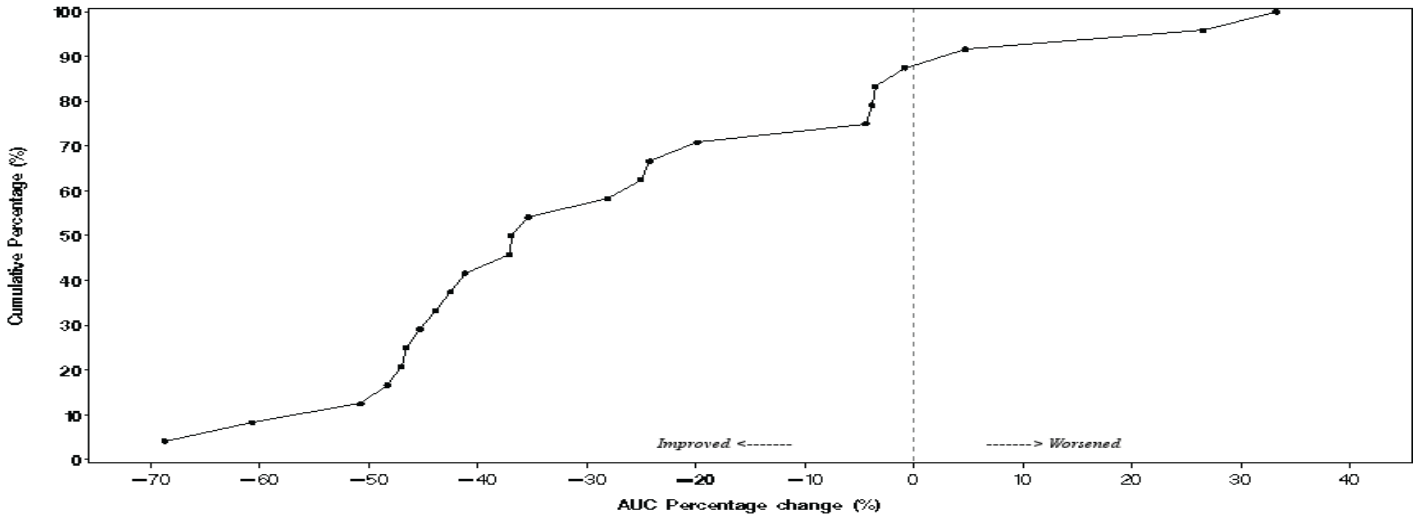
Twenty-five subjects were included in C-DM cohort of mITT population. Patients underwent 75-g OGTT at screening, on Day 1, at Weeks 6, 10, 16, 24 or early termination (ET) visits. The morning dose of short-acting insulin was held prior to test; other antidiabetic medications where allowed.

The study met this primary end point. Fifteen of 25[1] subjects with DM/impaired glucose tolerance in mITT population (60%) were responders in C-DM cohort and had a 25% or more decrease in $AUC_{glucose}$ at Week 24/ET from baseline value (95% CI lower bound, 42%) (Figure 2). Because the lower bound of the 95% CI was greater than 20%, this response rate of 60% was statistically significant. Biostatistician computed a 2-sided 95% confidence interval for the response rate: the lower bound of the 2-sided 95% confidence interval was 40.4%, still significant. The responder rates in the ITT and Completer populations were similar to the rates in mITT population and were statistically significant: 52% response rate (95% CI lower bound , 35%) and 65% response rate (95% CI lower bound , 44%), respectively.

Moreover, 21/24[1] (87.5%) subjects had some degree of improvement in glycemic control: the range of percent of improvement in $AUC_{glucose}$ varied from 0.8% to 69% in individual subjects. The cumulative distribution for percent reduction in $AUC_{glucose}$ at Week 24/ET is presented in Table 19. Only three patients had worsening in glucose control during the study: the percent of worsening in $AUC_{glucose}$ varied form 4.7% to 33%.

[1] There is a discrepancy between total number of subjects included in the efficacy population and number of subjects analyzed: 25 subjects were included in mITT population, but only 24 subjects had at least one post-baseline results of OGTT and, thus, were analyzed.

Figure 2. Cumulative Distribution Function for Percent Change in $AUC_{glucose}$ from Baseline to Week 24/ET: C-DM Cohort (mITT Population)



Source: Sponsor's figure 2, p. 75, Module 5, Vol 31, CSR 400,

Table 19. Cumulative Distribution Function for Percent Reduction in $AUC_{glucose}$ at Week 24/ET in C-DM Subjects (mITT population)

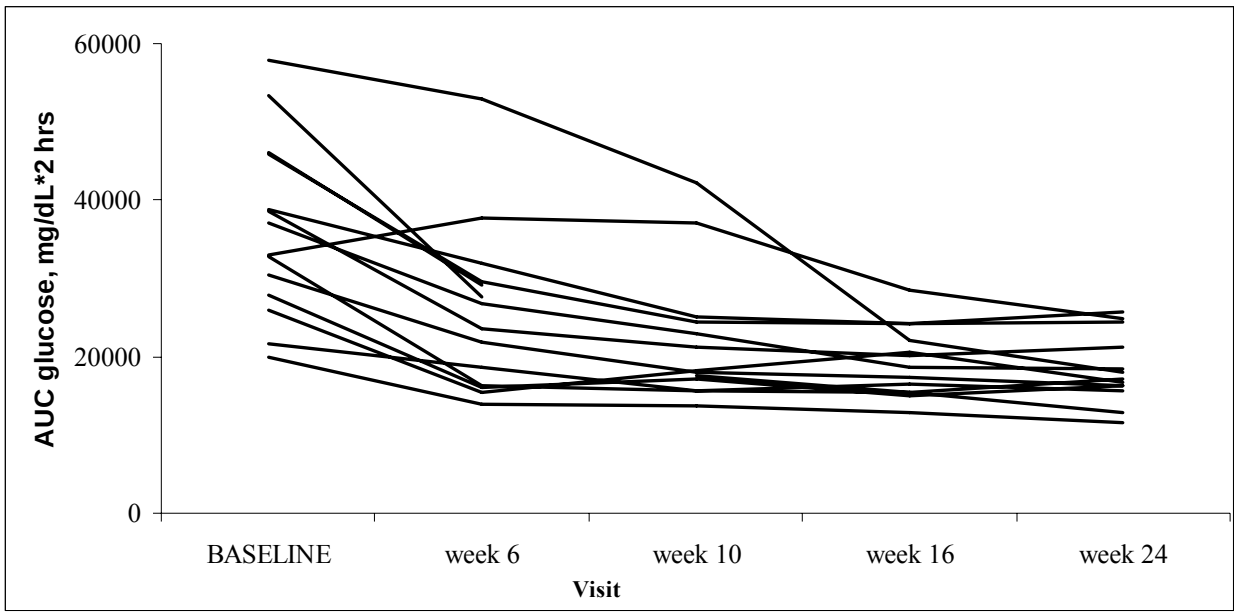
% Reduction from Baseline	Cumulative Distribution of Change, n (%)	Improved/ Worsened
-68.7	1 (4.17)	Improved
-60.6	2 (8.33)	Improved
-50.7	3 (12.50)	Improved
-48.2	4 (16.67)	Improved
-47.0	5 (20.83)	Improved
-46.5	6 (25.00)	Improved
-45.3	7 (29.17)	Improved
-43.9	8 (33.33)	Improved
-42.4	9 (37.50)	Improved
-41.2	10 (41.67)	Improved
-37.1	11 (45.83)	Improved
-36.9	12 (50.00)	Improved
-35.3	13 (54.17)	Improved
-28.0	14 (58.33)	Improved
-25.0	15 (62.50)	Improved
-24.2	16 (66.67)	Improved
-19.8	17 (70.83)	Improved
-4.4	18 (75.00)	Improved
-3.8	19 (79.17)	Improved
-3.5	20 (83.33)	Improved
-0.8	21 (87.50)	Improved
4.7	22 (91.67)	Worsened
26.5	23 (95.83)	Worsened
33.2	24^ (100.00)	Worsened

Source: Sponsor's table 15, Module 5, Vol 31, p. 73;
^One subject was excluded from mITT analysis (#20-022), because he did not have $AUC_{glucose}$ values post-baseline.

Medical officer's comment:
In this reviewer opinion, excluding patient #20-022 *from the responder analysis will not change the final results.*

This reviewer additionally evaluated whether the $AUC_{glucose}$ improvement was sustained in the responder subpopulation of C-DM cohort at each visit throughout the study. Six of 15 responders sustained the glucose control; $AUC_{glucose}$ in the other 9 subjects increased slightly at the intermittent visits as compared to the baseline values and to the values at the end of the study (Fig 3).

Figure 3. Plot of the Individual $AUC_{glucose}$ Values versus Time Profile (Responders in C-DM Cohort of mITT Population)



The mean baseline $AUC_{glucose}$ values of 30330.0 mg/dL*2 hrs decreased to 23655.0 mg/dL*2 hrs at Week 6 and to 22365 mg/dL*2 hrs at Week 24/ET (mean reduction of 27% over the course of the study). The mean change from baseline in $AUC_{glucose}$ was -8722 mg/dL*2 hrs (2-sided 95% CI = (-13184, -4260), p=0.0009) from a baseline mean of 30670 mg/dL. The earliest improvement in glucose control was observed at Week 6 visit (Fig 4). The mean reduction in $AUC_{glucose}$ over time in C-DM cohort (25 patients, mITT population) is displayed graphically in Figure 4; descriptive statistics are presented in Table 19.

Figure 4. Plot of Mean $AUC_{glucose}$ values versus Time Profile (C-DM Cohort, mITT Population)

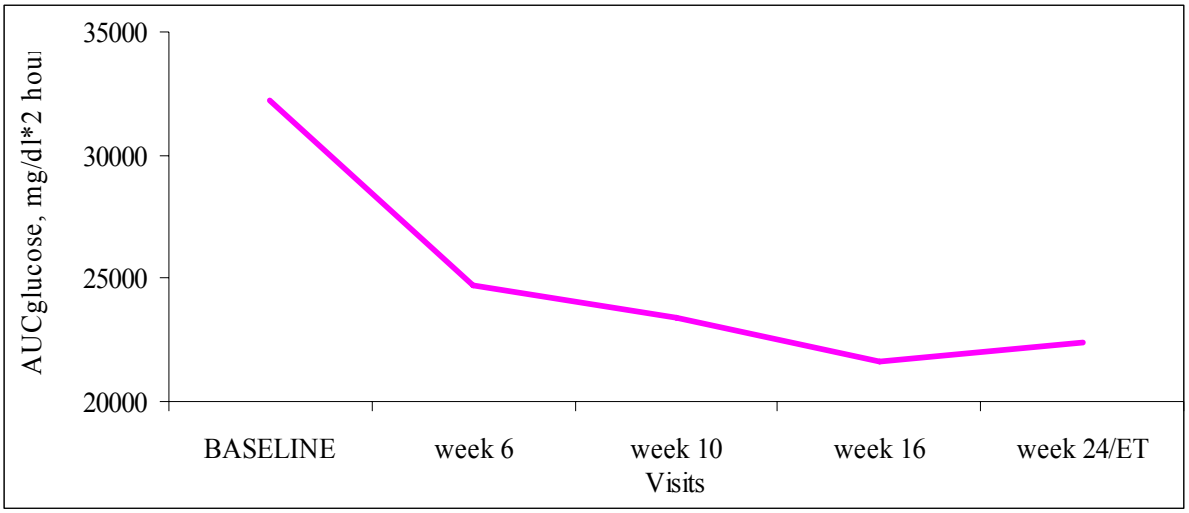


Table 20. Reduction in $AUC_{glucose}$ e in C-DM Subjects by Visit (mITT Population)

Visit	$AUC_{glucose}$ (mg/dL * 2 hours)	% Reduction from Baseline
Baseline, n	25	
Mean (SD)	32185.2 (10191.74)	
Median	30330.0	
Min, Max	18480, 57795	
Week 6, n	23	23
Mean (SD)	24703.0 (8823.31)	-21.776 (19.0642)
Median	23655.0	-19.469
Min, Max	13890, 52965	-50.69, 14.23
Week 10, n	20	20
Mean (SD)	23384.3 (8434.72)	-23.576 (22.6960)
Median	22327.5	-29.004
Min, Max	13710, 43500	-52.06, 35.58
Week 16 n	20	20
Mean (SD)	21625.5 (7398.09)	-29.186 (23.6989)
Median	19950.0	-31.099
Min, Max	12855, 44100	-61.82, 37.45
Week 24/ET, n	24	24
Mean (SD)	22365.0 (7757.35)	-27.038 (26.2438)
Median	20655.0	-36.129
Min, Max	11475, 42750	-68.67, 33.24

Source: Sponsor's table 14, Module 5, Volume 31, CSR 400, p. 72
Percent reduction = ([$AUC_{glucose}$ at Week XX - $AUC_{glucose}$ at baseline] / [$AUC_{glucose}$ at baseline]) × 100.
Negative number indicates improvement. Week 24/ET values include imputed data and are used for the efficacy analysis. The earliest changes in $AUC_{glucose}$ observed at 6-Week visit and $AUC_{glucose}$ values at the end of the study are highlighted.

In conclusion, patients with hypercortisolemia-induced DM or impaired glucose tolerance had significant improvement in glycemic control during Korlym treatment as demonstrated by decreased $AUC_{glucose}$ values at the end of the study.

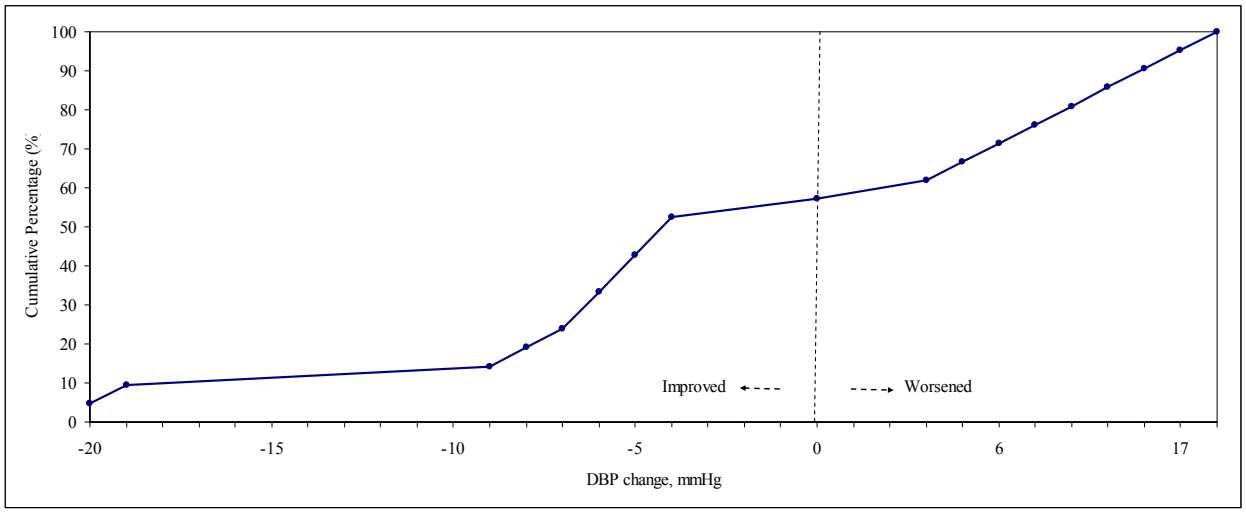
Medical Officer's comment:
To evaluate further whether such robust improvement in glycemic control is due purely to the treatment with Korlym and not to the other factors, the Sponsor was asked to evaluate $AUC_{glucose}$ and HbA_{1C} levels during the period of drug discontinuation and after the study drug was restarted. If the observed improvement in glycemic control is due to the effect of Korlym, $AUC_{glucose}$ and HbA_{1C} should increase during the drug discontinuation period and improve again after the study drug is restarted. The Sponsor responded that $AUC_{glucose}$ and HbA_{1C} levels were not evaluated during the treatment interruption period.

Primary Efficacy Outcome in C-HT cohort: the change in DBP from baseline to Week 24/ET.

Twenty one subjects with hypertension defined as SBP ≥ 140 mm Hg and/or DBP > 90 mm Hg were included in C-HT cohort. Blood pressure was measured at each study visit. The BP values were obtained after the subjects had been sitting for 5 minutes and refrain from the smoking and caffeine for 30 minutes. Two BP measurements differed by < 5 mm Hg within 2 minutes were required at all visits. If the two sequential measurements differed by > 5 mmHg, the pressure had to be retaken until consecutive measurements were within 5 mmHg of each other.

Even though the study met primary endpoint, the overall responder rate in patients with hypertension was lower than responder rate in patients with diabetes/impaired glucose tolerance. Only 8/ 21 subjects with hypertension in mITT population (38.1%) were responders and had ≥5 mm Hg decrease in DBP at Week 24/ET from baseline value (95% CI lower bound, 20.57%). Because the lower bound of the 95% CI was greater than 20%, this response rate of 38% was statistically significant. Biostatistician computed a 2-sided 95% confidence interval for the response rate that demonstrated that the lower bound of the 2-sided 95% confidence interval was 16.8% which fell below the margin. Of note, two subjects (#07-010 and #11-004) who met the responder criteria received spironolactone for treatment of hypokalemia; spironolactone is an antihypertensive drug and may reduce BP values. Furthermore, only half of patients in C-HT cohort (11/21 patients, 52%) had some improvement in DBP (decrease in DBP from 4 mm Hg to 20 mm Hg); the other half of the patients (10/21 patients, 48%) had worsening in DBP control at the end of the study (increase in DBP from 3 to 20 mm HG mm). DBP did not change by the end of the study in one patient. The cumulative distribution for change in DBP at Week 24/ET is presented in Table 21 and Figure 5.

Figure 5. Cumulative Distribution Function for mm HG in DBP from Baseline to Week 24/ET: C-HT Cohort (mITT Population)



Source: Sponsor's figure 14.2.8.1, module 5, vol 34.

Table 21. Cumulative Distribution Function for Change in Diastolic Blood Pressure at Week 24/ET in C-HT Subjects (mITT Population)

Change from Baseline (mmHg)	Cumulative Distribution of Change, n (%)	Improved/Worsened
-20.0	1 (4.76)	Improved
-19.0	2 (9.52)	Improved
-9.0	3 (14.29)	Improved
-8.0	4 (19.05)	Improved
-7.0	5 (23.81)	Improved
-6.0	7 (33.33)	Improved
-5.0	9 (42.86)	Improved
-4.0	11 (52.38)	Improved
0.0	12 (57.14)	No change
3.0	13 (61.90)	Worsened
5.0	14 (66.67)	Worsened
6.0	15 (71.43)	Worsened
8.0	16 (76.19)	Worsened
9.0	17 (80.95)	Worsened
10.0	18 (85.71)	Worsened
14.0	19 (90.48)	Worsened
17.0	20 (95.24)	Worsened
20.0	21 (100.00)	Worsened

Source: Sponsor's table 18, Module 5, Vol 31, CSR 400, p. 78

Moreover, the median DBP values in all C-HT cohort patients (21 patients, mITT population) were normal at baseline and decreased at the end of the study by 6 mm Hg (from 87 mmHg to 81 mmHg , respectively). The Sponsor stated that low DBP at baseline was secondary to the pre-inclusion aggressive hypertensive management. The mean DBP values were normal at baseline and did not change at the end of the study as compared to baseline values; as per Sponsor, the absence of the changes in mean DBP was due to the variability of diastolic blood pressure values throughout the study. As per biostatistician review: *"The mean change from baseline in dBP (mmHg) was -0.1 (2-sided 95% CI = (-4.6, 4.6), p=.98) from a baseline mean of 82.9. Therefore, across the two dBP endpoints, there was no statistical evidence of diastolic blood pressure lowering in the C-HT cohort".*

The changes in diastolic blood pressure values in the C-HT cohort are displayed graphically in Figure 6; descriptive statistics are presented in Table 22.

Figure 6. Mean DBP values Versus Time Profile: C-HT Cohort (mITT Population)

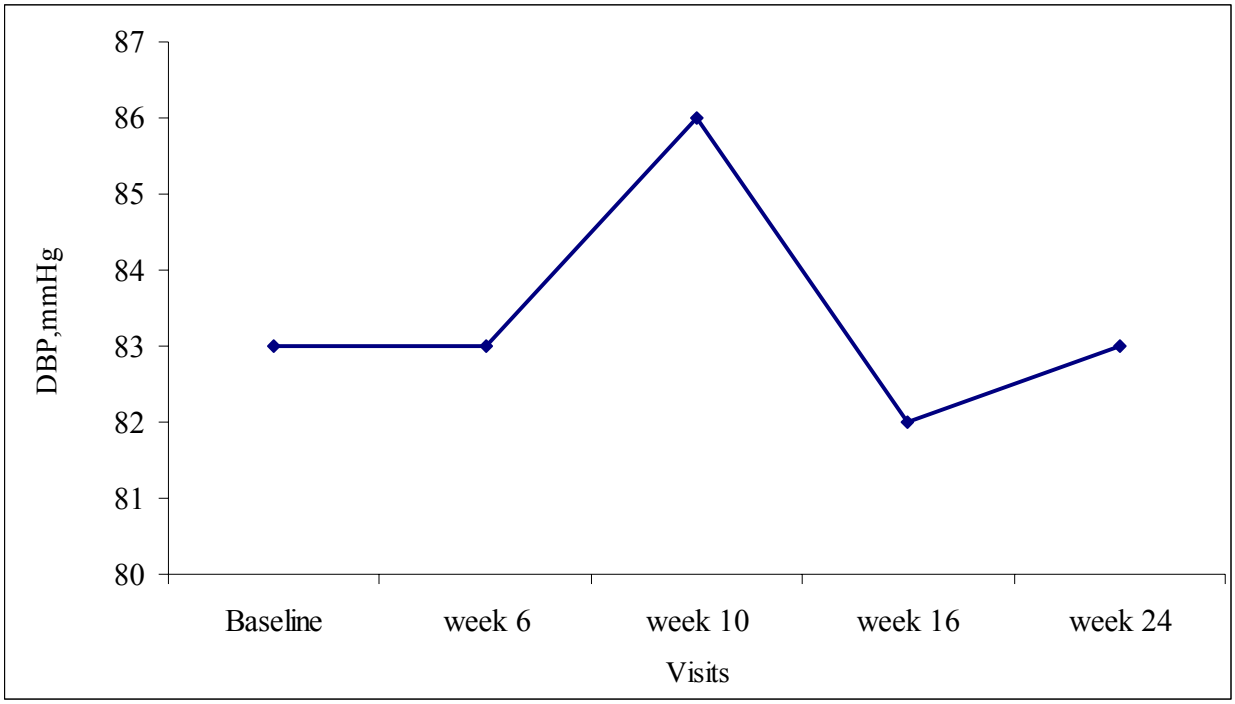


Table 22. Summary of Diastolic Blood Pressure in C-HT Subjects by Visit (mITT Population)

DBP, mm Hg	C-HT (n=21)	Change from Baseline
Baseline , n	21	
Mean (SD)	82..9 (11.42)	
Median	87	
Min, Max	62, 108	
Week 6 , n	20	20
Mean (SD)	82.9 (12.80)	-0.8 (10.12)
Median	86.5	0.5
Min, Max	47, 104	-16, 17
Week 10, n	18	18
Mean (SD)	86.1 (11.50)	1 (11.34)
Median	88.5	2.5
Min, Max	64, 103	-20, 21
Week 16, n	16	16
Mean (SD)	81.6 (12.48)	-3.2 (12.28)
Median	81	-4
Min, Max	56, 102	-28, 14
Week 24/ET, n	21	21
Mean (SD)	82.8 (13.16)	0 (10.74)
Median	81	-4
Min, Max	61, 108	-20, 20

Source: Sponsor's table 17, Module 5, Vol 31, CSR 400, p. 77
Values that increased as compared to baseline values highlighted in yellow, values that decreased as compared to baseline values highlighted in blue, values that remained unchanged as compared to baseline values highlighted in green.

The Sponsor additionally analyzed the changes in DBP in C-HT cohort after exclusion four patients who received spironolactone for the treatment of hypokalemia, because spironolactone is antihypertensive drug and may also decrease BP. Of these four subjects, one subject (# 07-006) had been on spironolactone prior to the study start and remained on this medication at a stable dose throughout the study. Two subjects (#07-010 and #11-004) were included in responder population for DBP:

- Subject #07-010 had a > 5 mmHg reduction in DBP before the treatment with spironolactone was initiated.
- Subject #11-004 was started on spironolactone after Week 6 visit, and there was an increase in DBP after Week 6 visit (at Weeks 8, 10, 12, 16, and 20), but decrease in DBP by > 5 mm Hg at Week 24.

Overall, no clinically meaningful difference was noted in DBP changes at the end of the study after exclusion of these four subjects (Table 23). Moreover, the comparison of the changes in DBP in patients with and without spironolactone treatment is difficult to interpret from the clinical stand point: three patients who were administered spironolactone after the initiation of Korlym treatment (and were excluded from the subgroup of patients *without spironolactone*

treatment at Week 24, n=17) were included in the subgroup of patients *without spironolactone treatment* at baseline (n=20).

Table 23. Diastolic Blood Pressure at Baseline and Week 24 Visit for Subjects with and without Spironolactone Treatment: C-HT Cohort mITT Population

DBP, mm Hg	All patients	Without spironolactone treatment
Baseline , n	21	20*
Mean (SD)	82.9 (11.42)	83.2 (11.63)
Median	87	87
Min, Max	62, 108	62, 108
Week 24 , n	20	17
Mean (SD)	82.9 (12.80)	81.6 (12.06)
Median	86.5	79
Min, Max	47, 104	66, 108
Week 24 change from baseline, n	21	17
Mean (SD)	0 (10.74)	-0.6 (10.91)
Median	-4	- 4
Min, Max	-20, 20	-20, 20

Source: Sponsor's table 14.2.6.1, module 5, vol32, modified.
* One patient was started on spironolactone prior to the onset of the treatment with Korlym.

Medical Officer's comments:
In this reviewer opinion, no clinically meaningful conclusion regarding improvement of the control of hypertension with Korlym treatment can be drawn. The efficacy of Korlym in the improvement of DBP and/or hypertension control is less prominent and difficult to interpret because of the following reasons:

1. *Overall, only 50% of patients had reduction in DBP with Korlym treatment; the other 50% of patients had worsening of the DBP values.*
2. *Hypertension in Study 400 is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure > 90 mmHg or pharmacologically treated hypertension, thus patients with normal DBP (but elevated SBP) were eligible for the study. The further decrease of normal DBP is of unknown clinical significance.*
3. *Some patients had normal DBP but elevated SBP values; the improvement in DBP pressure without controlling SBP does not decrease risk of cardiovascular morbidity and mortality and patients with normal DBP, but elevated SBP remained hypertensive.*
4. *Further analysis of BP values in C-HT cohort responders performed by this reviewer demonstrated that only 5/8 patients-responders were normotensive at the final visit (i.e. had normal DBP and SBP). The other three patients met criteria of hypertension at the end of the study; of these, two patients had worsening in SBP values at the end of the study (# 07-010 and 22-001). Patient # 07-010 had further increase in SBP from 153mm Hg at baseline to 162 mm Hg at end of the study. Patient #22-001 had normal SBP and DBP at baseline visit and was not on antihypertensive medications (but had elevated BP at screening visit to 146/93 mm HG), this patient became hypertensive at the end of the study (142/78 mm HG).*

5. *Patients in C-HT cohort had multiple protocol violations including the incorrect BP measurements and initiation or change in doses of antihypertensive medications. Five of 21 patients in C-HT cohort (non-responders) had two consequent BP values that differed by more than 5 mm. Four patients had increase or change in the dose of hypertensive medications while they were treated with Korlym (Table 24).*
6. *Two of 8 responders (#07-010) were on spironolactone during the study. Spironolactone was allowed to be administered for hypokalemia control, but it has pronounced antihypertensive effect too; thus may affect overall blood pressure control. The Sponsor stated that subject #07-010 had a DBP reduction before the treatment with spironolactone was initiated and subject had worsening of BP after spironolactone was initiated, but spironolactone may have played role in the maintenance of the BP control in both cases during the study.*
7. *Lastly, the antihypertensive effect of Korlym may be less obvious and Korlym may actually worsen the BP control because of the activation of mineralocorticoid receptors by elevated cortisol levels.*
8. *The interpretation of the BP changes in C-DM cohort with hypertension is also complicated because of the reasons listed above. Additionally, the major confounding factor was the adjustment of the antihypertensive medications during the study in this subpopulation. The dose changes or introduction of the new antihypertensive were allowed by the protocol in C-DM cohort. Overall, no clinically meaningful changes in DBP were observed in patients in C-DM cohort with hypertension at baseline: mean DBP decreased from the normal value (86 mm Hg) at baseline to 82 mm Hg at Week 24 visit.*

Table 24. Systolic and Diastolic BP Changes and changes in dose and/or number of antihypertensive medications in C-HT cohort (mITT population)

ID	Baseline, mm Hg		Week 24, mm Hg		Change in BP values at Week 24 from baseline, mm Hg		Antihypertensive medications (n of drugs)				
	SBP	DBP	SBP	DBP	DBP	SBP	Baseline	Stopped	Dose ↓	Dose ↑	Added
011004	107	69	94	61	-8	-13	2		1		
006002	143	84	133	79	-5	-10	5	3	2	1*	1*
008004	133	88	111	81	-7	-22	1		1		
024002	142	90	110	70	-20	-32	3		1		
016002	135	87	121	78	-9	-14	1				
003002	140	78	124	72	-6	-16					
007010	153	108	162	102	-6	9					
022001	127**	87	142	78	-9	15					
008005	120	87	129	93	6	9	1		1		
021001	99	63	125	66	3	26	1		1		
007006	141	77					3			2^	
007007	103	62	121	71	9	18	1				
008001	130	81	150	98	17	20	2				
016001	115	80					3				
008014	131	88	142	108	20	11	3		2	1	
010003	137	89	121	70	-19	-16	2				1
001003	127	77	121	85	8	-6	1			1	1
022003	131	87	170	97	10	39	1			1	1
022002	157	94	140	87	-7	-17					
024004	144	98	139	98	0	-5					

**Had elevated BP at screening: 146/93 mmHg; *Dose increase and new medication introduction occurred after the termination of the study drug; ^Dose increase occurred after the termination of the study drug. Aldactone dose was increased >4 weeks prior to Day 1; Data from patients-responders are highlighted in blue; elevated BP values are in red font.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary objectives of the Study 400 were to evaluate the effect of Korlym on signs and symptoms of Cushing's syndrome, on the $AUC_{glucose}$ changes or use of antidiabetic medications in C-DM cohort, on HbA_{1C} and insulin concentrations and insulin resistance, on body weight, on the diastolic and systolic blood pressure or use of antihypertensive medications in all patients participated in the study. Changes in HbA_{1C} levels or in the number or doses of antidiabetic or antihypertensive medications are important supportive endpoints and will be discussed in this section in detail. Such secondary endpoints such as an improvement in the Cushing's signs and symptoms as evaluated by a Drug Review Board are less robust endpoints in the evaluation of the disease control: the study was open-label, dose-titration study in which all participants received Korlym, thus reviewers were not truly blinded; some of the assessed categories including psychiatric and quality of life are subject of reporting bias that adds uncertainty of their findings and association with disease control; other assessed categories including clinical

appearance and strength assessment are not associated with improvement in mortality and morbidity associated with Cushing's syndrome. Lastly, each of eight categories was also evaluated as a separate secondary or exploratory endpoint.

Change in HbA_{1C} levels

The evaluation of HBA1C changes during Korlym treatment provides one of the major supportive evidences of the efficacy of Korlym in glycemic control in patients with DM/impaired glucose tolerance induced by hypercortisolemia. HbA_{1C}, unlike the OGTT, is not affected by such factors as diet, exercises and stress and provides more reliable and validated measure of long-term glycemic control. There was a robust improvement in HbA_{1C} levels by the end of the study. The mean reduction in HbA_{1C} levels from baseline to the end of the study was 1.14% (as per biostatistician review: 2-sided 95% CI = (-1.56, -0.65), p=.0001) in 21/25 patients in C-DM cohort (4 subjects did not have at least one postbaseline HbA_{1C} value). In these 21 subjects, the mean HbA_{1C} values decreased from 7.43 ± 1.52% to 6.29 ± 0.99%. Additionally, one more patient did not have HbA_{1C} measurements at baseline, but had elevated HbA_{1C} at screening visit (10.3%); the value decreased to 8.8% at Week 24 visit. Fourteen of 21 subjects had elevated HbA_{1C} levels at baseline (range 6.7%-10.4%); all of them had reduction in HbA_{1C} by the end of the study (by 0.4-4.4%) (Table 25). Of these, eight patient normalized HbA_{1C} at the final visit (HbA1C< 6.4%), and 7/8 patients were also responders for the primary endpoint (reduction in $AUC_{glucose} \geq 25\%$). Overall changes in HbA1C were consistent with the reduction in $AUC_{glucose}$ observed in patients: 11/14 patients with improved HbA1C at the end of the study were also the responders for the primary end-point, two more patients had decrease in $AUC_{glucose}$ by 0.8% and 3.5%. Only one patient with HbA1C reduction at the final visit had increase in $AUC_{glucose}$ by 26% at the end of the study. This Medical Officer also reviewed the individual values of HBA1C at intermittent time points during the study; general pattern of the HbA1C changes was consistent with overall findings.

Table 25. HbA_{1C} and % of $AUC_{glucose}$ Changes from Baseline to Week 24 Visit in Patients with Elevated HbA_{1C} at Baseline in C-DM Cohort (mITT Population)

ID	HbA_{1C}, %			$AUC_{glucose}$ change at Week 24 from baseline, %
	Day 1	Week 24	HbA1C 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

Responders for $AUC_{glucose}$ are highlighted; Normal HbA_{1C} values in red;
*This patient had increase in Insulin dose during the study and listed as protocol violator (refer to Section 3.2)

Responder Analysis for Subjects with Either at Least a 25% Reduction in $AUC_{glucose}$ or Reduction in Antidiabetic Medications at Last Visit in C-DM Cohort

Overall, reduction in doses and/or number of antidiabetic medications at the end of the study in patients in C-DM cohort was consistent with the reduction in $AUC_{glucose}$ and HbA_{1C} observed in the same patients. Total 18/25 (72%) patients had a reduction in $AUC_{glucose}$ of $\geq$ 25% and/or in number/doses of antidiabetic medications in the C-DM cohort of mITT population (95% CI: 50.6%, 87.9%):

- 15/ 18 patients were responders in C-DM cohort and had $\geq$ 25% reduction in $AUC_{glucose}$ at Week 24 from baseline; of these, 4 subjects also had a reduction in dose /numbers of antidiabetic medications
- 3/ 18 patients had a reduction in doses of antidiabetic medications only; of these, $AUC_{glucose}$ increased in 2/3 patients and decreased in 1/3 patient by 3.5%.

Overall, 19/25 subjects in the C-DM cohort were taking at least one antidiabetic medication, of these seven subjects had a reduction in antidiabetic medications. Four of seven subjects who had reduction in the number or dose of antidiabetic medications also had a reduction in $AUC_{glucose} \geq$ 25%; 3/7 subjects had a reduction in number/dose of antidiabetic medications only. Twelve of 15 subjects were treated with insulin at baseline; of these, five subjects had a decrease in the insulin dose at the end of the study. Subjects with reductions in antidiabetic medications are summarized in Table 26.

Table 26. Reduction in Antidiabetic Medications (mITT Population)

Drug	Baseline visit		Last visit	
	Number of subjects	Median total daily dose	Number of subjects with dose reduction	Median reduction in total daily dose
Insulin	12	88 units	7**	48 units
SU	4	9 mg	1*	15 mg
Metformin	10	1500 mg	0	
Sitagliptin	5	100 mg	0	
Exenatide	1	20 mcg	0	

Source: Sponsor's table 21, Module 5, Vol 31, CSR 400, p. 82, modified
*Had reduction in both: metformin (from 20 mg total daily dose to 5 mg total daily dose by Week 10) and insulin
** 5 patients had ≥ 50% reduction in median daily dose

Responder Analysis for Change in Diastolic Blood Pressure or in Antihypertensive Medications in all subjects with Hypertension at Screening (C-HT and C-DM cohorts)
Overall, 87% (40/46) subjects in mITT population had hypertension at baseline. Seventeen of 40 subjects (42.5%) were responders for a reduction in DBP of ≥ 5 mm Hg at Week 24/ET from baseline: 11/19 subjects with hypertension in C-DM cohort and 8 subjects in C-HT cohort, respectively. Eleven of 40 patients (27.5 %) were responders for a reduction in number/doses of antihypertensive medications at Week 24 visit from baseline. Overall, 21 subjects were responders for this secondary endpoint and had ≥5 mm Hg reduction in DBP or reduction in antihypertensive medications (95% CI, 36.13%, 68.49%) at Week 24 visit from baseline.

Medical Officer's comments:
1. During the conduction of Study 400 the Sponsor realized that the baseline BP in subjects enrolled in C-HT cohort was not as high as expected because of the aggressive management of hypertension in patients with Cushing's syndrome with antihypertensive medications. Therefore, the Sponsor submitted (b) (4) *In the response to* (b) (4) *Additionally, Division pointed out that the* (b) (4)

2. The introduction/ change in antihypertensive drugs were not allowed in C-HT cohort, but was allowed in C-DM cohort, thus majority of patients in C-DM cohort had introduction of new or change in the dose of antihypertensive medications during the evaluation of this secondary endpoint. Therefore, whether improvement in BP control in overall population (C-DM and C-HT) was due to Korlym treatment or to the introduction of the new antihypertensive medications or change in the dose of antihypertensive medications in the subgroup of patients with DM (C-DM cohort) is not clear.

Change in Body Weight
Progressive weight gain is one of the commonest features of Cushing's syndrome and is due to the accumulation of fat in the upper body and face (central obesity) and fluid retention; weight

gain usually improves after the successful treatment of hypercortisolemia. All but one patient in mITT population (45/46 patients) had increased body weight at baseline (mean weight - 99.5 kg; BMI was 35.7 kg/m2). Overall tendency towards weight loss was observed with Korlym treatment during the study: 36/46 subjects (78%) lost weight at the end of the study (20/25 subjects in C-DM cohort and 16/21 subjects in C-HT cohort). Mean percent of weight change in 36 subjects was 8.3% ± 5.9%; 24/36 patients lost ≥ 5% of baseline weight (12/24 subjects lost ≥ 10% of their baseline weight). Subjects in C-DM cohort had slightly greater weight loss than subjects in C-HT cohort (8.7% vs. 7.7%, respectively). There were no body weight outliers, and changes in median values were similar to the mean values changes.

Ten of 46 subjects (22%) gained weight (5 patients in C-DM and C-HT population, each); mean percent of weight gain was 3.6%. Subjects in C-DM cohort had greater weight gain than subjects in C-HT cohort: 5.1% and 2.12% (median 2.9 and 2.2%), respectively. The percent change from baseline body weight at Week 24 for the mITT population is summarized in Table 27.

Table 27. Percent Change in Body Weight from Baseline to Week 24 (mITT Population)

Percent Change in Body Weight	C-DM	C-HT	Overall
Overall	n=25	n=21	n=46
Mean (SD)	-5.967 (8.2204)	-5.388 (6.5194)	-5.703 (7.4172)
Median	-6.595	-5.114	-5.406
Range	-21.29, 13.29	-18.92, 4.26	-21.29, 13.29
Subjects who lost weight	n=20	n=16	n=36
Mean (SD)	-8.746 (6.2668)	-7.736 (5.5971)	-8.297 (5.9165)
Median	-7.79	-6.136	-7.414
Range	-21.29, -0.54	-18.92, -1.37	-21.29, -0.54
Subjects who gained weight	n=5	n=5	n=10
Mean (SD)	5.148 (5.0843)	2.127 (1.5456)	3.638 (3.8841)
Median	2.9	2.19	2.817
Range	0.22, 13.29	0.48, 4.26	0.22, 13.29

Source: Sponsor's table 22, Module 5, Vol 31, CSR 400, p. 83.
Body weight values that decreased at the end of the study are highlighted in yellow, body weight values that increased at the end of the study are highlighted in blue.

Systolic Blood Pressure

The change in systolic blood pressure at Week 24 visit from baseline in patients with hypertension at baseline (all mITT population) is summarized in Table 28 and is displayed graphically in Figure 7.

No clinically meaningful improvement in SBP was observed: mean decrease in SBP was 2.5 mm Hg at the end of the study from baseline (95% CI, -8.56, 3. 66). Subjects in C-DM cohort with hypertension had a higher mean systolic blood pressure at baseline (138 mm Hg) and a greater decrease in SBP (-5.6 mm Hg) when compared to C-HT subjects (130 mm Hg and +0.4 mm Hg, respectively). Of note, change in dose or introduction of the new antihypertensive medications was not allowed in C-HT cohort, but was allowed in C-DM cohort; thus, the greater decrease in SBP in C-DM cohort might be due to the aggressive antihypertensive therapy during the study, and not to the effect of Korlym on BP. Additionally, the changes of 2.5 mm Hg in SBP are too

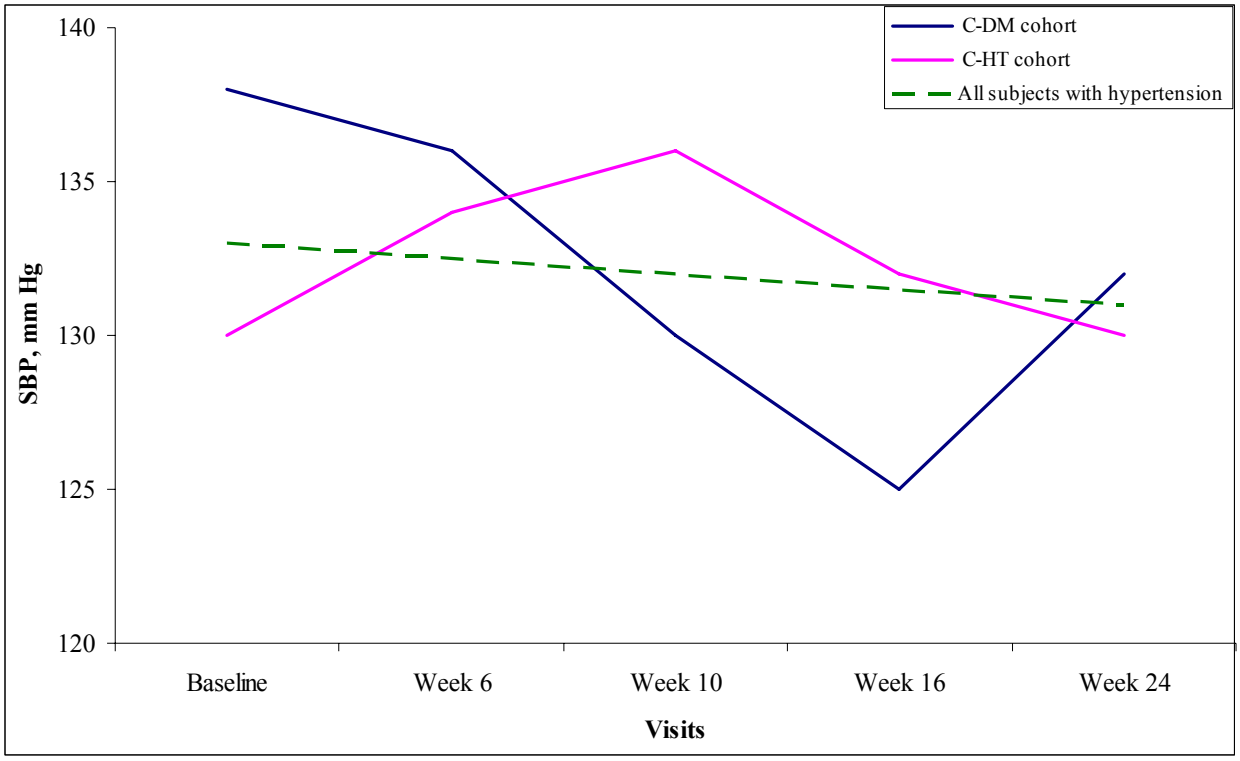
small and of unknown clinical significance, SBP and/or DBP values were elevated at the end of the study in the majority of subjects, and patients continued to carry diagnosis of hypertension at the end of the study. Lastly, multiple protocol violations including incorrect measurements of BP (the difference in two consecutive BP readings of > 5 mm Hg) and change of dose or introduction of the new antihypertensive medications during the study preclude meaningful interpretation of the small changes in SBP.

Table 28. Summary of Change from Baseline in SBP: All Subjects with Hypertension at Screening (mITT population)

SBP, mm Hg	**C-DM** n=25	**C-DM with HT** n=19	**C-HT** n=21	**All subjects with HT** n=40
Baseline				
Mean (SD)	133 (22.8)	138 (24)	129 (16)	133 (20.5)
Median	130	141	131	134
Range	100, 181	100, 181	99, 157	99, 181
Week 24				
Mean (SD)	129.8 (16.5)	132 (16.7)	130 (19)	131 (17.7)
Median	131	132	125	129
Range	105, 160	105, 160	94, 170	94, 170
Week 24 change from baseline				
Mean (SD)	-3.8 (18.70)	-5.6 (19.5)	0.4 (18.7)	-2.5 (19)
Median	-2	-2	-3	-2.5
Range	-52, 32	-52, 32	-32, 39	-52, 39

Source: Sponsor's table 14.2.13.1, Module 5Vol 32.
Changes in SBP at Week 24 visit are highlighted.

Figure 7. Mean SBP values Versus Time Profile: All Patients with Hypertension at baseline (mITT Population)



Key Secondary Efficacy Analysis

The key secondary efficacy analysis included an evaluation of changes in signs and symptoms of Cushing's syndrome conducted by DRB comprised of three independent experts on Cushing's syndrome. The DRB members were blinded to the visit sequence and to the patient's dose of Korlym. There were eight categories of assessment:

1. Assessment of glucose homeostasis
2. Assessment of blood pressure
3. Assessment of lipids
4. Change in weight and body composition
5. Clinical appearance (e.g., acne, hirsutism, striae, Cushingoid appearance)
6. Strength assessment
7. Psychiatric and quality of life assessment
8. Metabolic bone assessment

The clinical improvements in patients' signs and symptoms of Cushing's syndrome were evaluated by responder analysis. A responder was defined as a subject whose median reviewer score was +1 at any reviewed visit after baseline visit.

Overall clinical status improved in 87% of subjects (40/46 patients) in mITT population as assessed at any visit. Because the lower bound of the 95% CI was greater than 30% (76%), these response rates were statistically significant. The responders rate was high and statistically significant when patients in C-DM and in C-HT cohort were evaluated separately (23/25 patients, 92% (lower bound 95% CI, 76%) and 17/21 patients, 81% (lower bound 95% CI, 62%,

respectively). The median DRB reviewer scores for the clinical improvement by study visits are presented in Table 29. The highest proportion of patients with scores +1 was observed at Week 24 visit, 33/46 patients (72%), including 19/25 patients (76%) in C-DM cohort and 14/21 patients (66%) in C-HT cohort. Overall, nineteen subjects had score of +1 at Week 6 visit; of these, 11 subjects sustained this improvement throughout the study. Six subjects with the improvement in scores at Week 10 visit sustained this improvement till the end of the study. Three subjects had a non-sustained improvement during the study: a median score was +1 prior to Week 24 visit and 0 at Week 24 visit. Only one subject (# 22-003) was rated as "worse than at baseline" (score -1) at Week 24 visit.

Table 29. Median Scores of Data Review Board for Clinical Improvement by Visit

Scores	C-DM, n (%)	C-HT, n (%)
Week 6	n=24	n=20
Score 0 (no improvement)	12 (50)	13 (65)
Score +1 (Improvement	12 (50)	7 (35)
Week 10	n=20	n=18
Score 0 (no improvement)	10 (50)	9 (50)
Score +1 (Improvement	10 (50)	9 (50)
Week 16	n=20	n=16
Score 0 (no improvement)	13 (65)	5 (31)
Score +1 (Improvement	7 (35)	11 (69)
Week 24	n=21	n=19
Score 0 (no improvement)	2 (10)	4 (21)
Score +1 (Improvement	19 (90)	14 (74)
Score -1 (Worsened)	0	1 (5)

Source: Sponsor's table 20, Module 5, Vol 31, CSR 400, p. 81, modified.

Medical Officer's comments:
1. The study was an open label study, thus the reviewers were not truly blinded. The 7/8 clinical parameters (except clinical appearance) are also discussed individually in sections 6.1.5 and 6.1.6.
2. As per biostatistician reviewer "the definition of a Responder in the key secondary efficacy variable: "A responder was defined as a subject whose median reviewer score was + 1 at any reviewed visit after baseline through Week 24/ET" with the phrase "at any reviewed visit," gives multiple opportunities for a success and is not as dependable as a response at any one time-point". Therefore, the improvement in this key variable looks very high and results should be interpreted with caution.

6.1.6 Other Endpoints

All other efficacy endpoints were exploratory in Study 400 and include waist circumference changes, body composition changes, insulin levels changes, bone mineral density and bone mineral markers changes, muscle strength, cognitive and psychiatric function, quality of life (QOL), and thombin-antithrombin (TAT), e-selectin, and adiponectin levels. Additionally, efficacy endpoints were also exploratory in Study 415 and were based on Physician's Global Assessment of Disease and Subject Rated Disease Severity. Such endpoints as changes in insulin sensitivity, and body composition were supportive of the primary findings of the efficacy of

Korlym in the improvement of the glycemic control. Changes in bone mineral density, in muscle strength, and in cognitive and psychiatric function and in quality of life (QOL) were inconclusive most likely because of the small number of evaluated patients, short duration of the treatment and wide range of the baseline and final scores. The other endpoints such as TAT, adiponectin and e-selectin levels were of the scientific interest only. All exploratory endpoints will be discussed briefly only in this section.

Insulin levels

Insulin resistance, hyperinsulinemia and glucose abnormalities are almost invariably present in patients with Cushing syndrome and improve with successful treatment of hypercortisolemia (Loriaux, 2001). Thus, the Sponsor analyzed effect of Korlym on insulin levels; the insulin levels were analyzed separately in subgroups of patients who were treated with and without insulin. Overall, there was an improvement in insulin levels and insulin resistance in subjects with Cushing's syndrome at the end of the study; the observed improvements were consistent with the overall improvement in the glycemic control. Subjects in the C-HT cohort and subjects in the C-DM cohort who were not using insulin had similar baseline insulin levels during OGTT. $AUC_{insulin}$ values in subjects who were not on insulin (13 subjects in C-DM cohort and 21 subjects in C-HT cohort) decreased by 35% at Week 24 visit; the first decline in $AUC_{insulin}$ values was observed at Week 6 visit (Table 30). Subjects in C-DM cohort had greater insulin resistance at baseline (evaluated by Homeostasis Model Assessment of Insulin Resistance (HOMA-IR)) than subjects in the C-HT cohort. The HOMA-IR values improved in both cohorts; the earliest improvement in insulin resistance was observed at the same time when the earliest improvement in $AUC_{glucose}$ values was observed- at Week 6 and persisted throughout the study (Table 31).

Table 30. Summary of Changes from Baseline in $AUC_{insulin}$ by Visit (Population)

$AUC_{insulin}$, uU/mL x 2hr	**Subjects on insulin therapy**	**Subjects not on insulin therapy**	**Total**
Baseline, n	8	33	41
Mean	10275	12081	11729
Min, Max	2100, 24045	1155, 30615	1155, 30615
Week 6, n	10	32	42
Mean	7454	7575	7549
Min, Max	2175, 14880	1245, 23595	1245, 23595
Week 6 change, n	7	31	38
Mean (SD)	-3497	-3706	-3667
Min, Max	-10920, 1110	-15750, 2490	-15750, 2490
Week 24/ET	12	33	45
Mean (SD)	6300	7501.36	7181.00
Min, Max	2220, 19890	1800, 23595	1800, 23595
Week 24 change, n	8	32	40
Mean	-4834	-4239.8	-4359
Min, Max	-14775, 5250	-17460, 3435	-17460, 5250

Source: Sponsor's table 26, Module 5, Vol 31, CSR 400, p. 94, modified
The earliest decrease in insulin levels and overall changes in $AUC_{insulin}$ at the end of the study are highlighted.

Table 31. Summary of HOMA-IR Results by Visit and Population (C-HT subjects and C-DM Subjects Not Taking Insulin)

Visit	C-DM cohort (no insulin therapy)					C-HT cohort				
	Mean	Median	25th percentile	25th percentile	IQR	Mean	Median	25th percentile	25th percentile	IQR
Baseline	**8.6**	**5.1**	4.7	5.7	1.1	5.3	4.1	2.5	7.1	4.7
Week 6	5.5	3.5	2.9	6.4	3.5	3.5	2.4	1.8	3.8	1.9
Week 10	6.1	4.4	2.4	6	3.6	3.4	2.3	1.8	3.2	1.4
Week 16	4.2	3.5	2.8	5.2	2.4	2.6	2.2	1.6	2.7	1.1
Week 24	**3.6**	**3.1**	2.1	5	2.9	2.4	2.2	1.9	2.8	0.9

Source: Sponsor's table 27, Module 5, Vol 31, CSR 400, p. 96,.
The baseline and final values of insulin resistance are highlighted.

Waist Circumference

The truncal obesity is a common feature of Cushing's syndrome and is associated with increased waist circumference. Majority of enrolled patients in mITT population had large mean waist circumference 119 ± 20.3 cm (median 115 cm, range 88.5-178.4 cm). Patients in C-DM cohort had more pronounced truncal obesity (mean waist circumference 124 ± 21.7 cm, median 120 cm, range 97.9-178.4 cm) as compared to the patients in C-HT cohort (mean waist circumference 111 ± 15.8 cm, median 104 cm, range 88.5-153.5 cm). In overall mITT population, males had greater baseline waist circumference than females (120.4 ± 25.7 cm and 117.9 ± 18.5 cm, respectively) and had a greater decrease in waist circumference by Week 24 (mean change: 8.44 cm ± 5.9 cm and 6.78 cm ± 5.8cm, respectively). Patients in C-DM cohort had greater waist circumference than patients in C-HT cohort at baseline; reduction in waist circumference at final visit was greater in males in C-DM cohort. Overall, there was some improvement in waist circumference observed at the end of the study, but the definite conclusion can not be drawn at this time; the subgroups of patients were small, precluding meaningful interpretation of the findings. A summary of waist circumference changes in is presented in Table 32.

Table 32. Summary of Change from Baseline in Waist Circumference (mITT Population)

Waist Circumference (cm)	Males			Females		
	C-DM (n=6)	C-HT (n=8)	All (n=14)	C-DM (n=19)	C-HT (n=13)	All (n=32)
Baseline (cm) Mean (SD)	**132 (32.8)**	**111 (15.6)**	**120 (25.7)**	**122.4 (18.9)**	**111.3 (16.5)**	**117.9 (18.5)**
Median	122	109	115	120	103	115
Min, Max	98, 178	88 , 140	88, 178	99, 162	94, 153	94, 162.
Week 24 (cm) Mean (SD)	121 (29.421)	105.39 (17.663)	111.98 (23.734)	115.8 (19.6)	104 (17.3)	111 (19.3)
Median	107.3	102.95	104.4	113.3	104.7	109.5
Min, Max	95 , 161	79 , 139	79 , 161	87, 160	84 , 146	84 , 160
Change (cm) Mean (SD)	**-11.7 (7.5)**	**-5 (2.7)**	**-8.4 (5.8)**	**-6.6 (5.5)**	**-7.1 (6.4)**	**-6.8 (5.8)**
Median	-10.8	-6.35	-7.35	-7	-7	-7
Min, Max	-23 , -3	-9 , -1	-23 , -1	-17, 3	-19, 6	-19, 6

Source: Sponsor's table 24, Module 5, Vol 31, CSR 400, p. 88
Baseline values and changes in waist circumference at the end of the study are in red font.

Assessment of Body Composition

The change from baseline in body composition in mITT population at Week 24 is summarized in Table 33. The improvement in body composition was observed during the course of the study; this improvement was consistent with the other improvements in Cushing's signs and symptoms observed during the study such as improvement in glycemic control, decrease in body weight and waist circumference. Overall, the mean percent total body fat decreased by 3.6% (from 42.3% at baseline to 38.7% at the end of the study), and total body fat mass declined by 5609 g (13.9%) from baseline. Patients in C-DM cohort had higher total body fat at baseline compared to patients in C-HT cohort (44277 g and 36218 g, respectively) and had a greater reduction in total body fat at Week 24 visit. The regional fat in android region decreased by 17.1% (6056 g to 5021 g), respectively, at the end of the study; increased android fat distribution is associated with coronary heart disease and insulin resistance.

Table 33. Summary of Change from Baseline in Body Composition by Visit

Body composition		**C-DM (n=19)**	**C-HT (n=18)**	**Total (n=37)**
, % of total body fat	**Baseline** Mean (SD)	43.3 (6.8)	41.12 (7.1)	42.3 (7)
	Median	43.4	40.9	43
	Min, Max	25.5, 58.6	26, 53.4	25.5, 58.6
	Change Mean (SD)	-3.7 (3.6)	-3.5 (3.2)	-3.6 (3.3)
	Median	-3.2	-3.6	-3.5
	Min, Max	-11.1, 0.5	-11.2, 2.1	-11.2, 2.1
Total Body Fat (g)	**Baseline** Mean (SD)	44277.4 (-17346)	362184 (-11486)	40356.6 (-15146)
	Median	40117.9	35279.2	36384.8
	Min, Max	20272.5, 79606	22338.1, 62880	20272.5, 796068
	Change Mean (SD)	-6177.6 (-5438.4)	-5009. 3 (-5586.9)	-5609.2 (-5466.1)
	Median	-4168.2-	-3731.26	-4157.24
	Min, Max	-16388, 1943.5	-23675.7, 2736	-23675.7 , 2736
% Android fat	**Baseline** Mean (SD)	**6.6** (1.3)	**6** (1.4)	**6.3** (1.4)
	Median	6.8	5.9	6.4
	Min, Max	3.1, 8.5	3.7, 8.2	3.1, 8.5
	Change Mean (SD)	**-0.826** (0.81)	**-0.706** (0. 8)	**-0.8** (0.8)
	Median	-0.8	-0.4	-0.5
	Min, Max	-2.6, 0.5	-2.3, 0.2	-2.6, 0.5
Android fat, g	**Baseline** Mean (SD)	**6798.9** (-2880.7)	**5272.4** (-1838)	**6056.3** (-2518)
	Median	6319.7	4897.8	5535.5
	Min, Max	2510, 13346.7	2423, 8933	2423, 13346.7
	Change Mean (SD)	**-1192.8** (-1001.3)	**-869.7** (-1044)	**-1036** (-1021)
	Median	-1099	-583.5	-740.7
	Min, Max	-3533, 35.5	-4064.6, 266.4	-4064.6, 266.4

Source: Sponsor's table 25, Module 5, Vol 31, CSR 400, p. 91.
Improvement in android fat content is in red font.

Total lean mass did not change during the study. Mean total body lean mass in subjects in C-DM cohort was 53779 g at baseline (range: 33398 g, 82765 g) and increased by 209 g (range: -7748 g, +8016 g). Mean total body lean mass in subjects in C-HT cohort was 48600 g at baseline (range: 35366 g, 73397 g) and decreased by 31g (range: -6672 g, +5477 g).

Bone Mineral Density

Osteoporosis and osteopenia are common features of Cushing's syndrome. Thus, the Sponsor evaluated changes in BMD during treatment with Korlym. DEXA scan was performed at screening and at Week 24 visits. The mean T-scores at the lumbar spine, total hip, and femoral neck were in the normal range at baseline (-0.73, -0.64, and -0.99, respectively) although the range varied considerably (3.0 to -3.1). By the end of the study, BMD declined at the lumbar spine, at the total hip and at the femoral neck: mean change was -3.1% (from 1.011 gm/cm^2 at baseline to 0.979 gm/cm^2 at the end of the study), -3.1% (from 0.902 at baseline to 0.874 g/ cm^2 at the end of the study), and -3.6% (from 0.786 at baseline to 0.758 gm/ cm^2 at the end of the study), respectively. Of note, because the bone mineral density worsened at the end of the Study 400, the Sponsor evaluated bone mineral density parameters further in the Study 415 (as safety parameters). The DXA scans were performed every 6 months (after IRB approval of the amendment 4 of the protocol on November, 2010). Overall, the mean BMD values obtained in Study 415 (mean follow-up period 21 months) worsened in lumbar spine, femoral neck and total hip regions as compared to the values obtained at the baseline in Study 400 (the mean change was -0.12% ± 4.20%, -4.01 % ± 3.22%, and -5.91 % ± 2.67%, respectively). There was additional loss in BMD at the total hip and at the femoral neck: the mean BMD values at the femoral neck and at the total hip were lower during the last evaluation in Study 415 compared to evaluation at baseline in Study 400 (0.7605 gm/ cm2 and 0.7952 gm/cm^2, 0.8532 gm/cm^2 and 0.9283 gm/cm^2, respectively).

Medical Officer's comments:
The observed decline in BMD might be due to the short period of observation (< 1 year) and small number of patients. Additionally, the vitamin D status was not evaluated in these patients; patients with Cushing's syndrome frequently have abnormal vitamin D levels that might affect the BMD values as well. Finally, there is evidence that successful treatment of hypercortisolemia may improve, but not normalize BMD (Nieman et al, 2008). Overall, no clinically meaningful conclusion regarding effect of Korlym on bone mineral density can be drawn at this time. A longer period of observation might be required to detect clinically meaningful changes.

Bone Turnover Markers

There was no clinically meaningful trend towards increase or decrease in bone markers levels throughout the study. Osteocalcin and NTx levels were within normal range at baseline, increased through Week 16 and slightly decline at Week 24, but remained within normal range. There were no changes in bone-specific alkaline phosphatase levels

Psychiatric and QOL assessment

Depression, cognitive dysfunction and decreased quality of life (QOL) are commonly associated with Cushing's syndrome.

Cognitive function was evaluated by Trial Making test that consisted of part A and B; a lower score indicates better functioning (the normal scores for patients 45-54 years old is 31 and 64 seconds for part A and B, respectively). Overall, all patients in mITT population (mean age 45.4 years) had normal cognition at baseline: median scores were 27.5 seconds (range 10-88 sec) and 69 seconds (range 22-229 sec) for parts A and B, respectively. The scores remained within normal range but slightly decreased by the end of the study (to 25.5 seconds (range 12-50 sec) and 57 seconds (range 22-270 sec), respectively). Overall, no meaningful conclusion can be drawn about the improvement in cognitive function in patients with Cushing's syndrome at this time; the changes in final scores were small, and patients had overall normal cognitive function at baseline.

The severity of depression was assessed by BDI-II, one of the most widely used instruments for measuring the severity of depression. The BDI-II scores of 20-28 indicative of moderate depression and of 29 - 63 are indicative of severe depression. The overall baseline score in mITT population was consistent with mild depression (median score 14.5, range 0 - 49); the score slightly decreased by 3 points at Week 24. The median score in the 25 subjects with at least mild depression at baseline (score 23) decreased by 6 points at Week 24. The median decrease in BDI-II scores in subjects with moderate and severe depression at Week 24 visit was 5.5 points. Overall, due to the small number of patients evaluated, and wide range of the scores at baseline and at the end of the study no meaningful conclusion can be made.

Quality of life was assessed by the SF-36. Sponsor stated that QOL improved with Korlym treatment. Sponsor concluded that that subjects in the study had significant health status burden at baseline and that, on average, their health status significantly improved with treatment. At baseline, mean SF-36 scores were: for the Physical Component Summary (PCS) - 34.9 ± 10.95 and for the Mental Component Summary (MCS) - 40.0 ± 14.5. The both scores improved at Week 24 visit: mean PCS score increased by 3.2 ± 8.32 points and mean MCS scores increased by 4.6 ± 10.7 points. Sponsor stated that changes of 3.1 points were considered meaningful.

Strength Assessments
One of the common Cushing's syndrome features is myopathy and peripheral muscle weakness. The muscle strength was evaluated by hand-grip test and sit-to stand-test. Additionally, strength was also evaluated on the Physical Function scale of the SF-36. Overall, no clinically meaningful improvement in muscle strength was reported in the population of patients with Cushing's syndrome.

Patients had normal strength in upper extremities at baseline (mean hand-grip test score of 53.5 pounds ± 28.56 (range 0 - 124 pounds)). As per Sponsor, mean hand-grip strength values showed a small downward trend over the course of the study; however, there was a large degree of intra-subject variability. Baseline median sit-to stand score was 12.0 seconds (range 6.1 – 107

seconds) in overall mITT population; the mean sit-to-stand scores decrease by Week 10 -Week 24; however, there was little change in median scores, suggesting that only few subjects had large improvements in the lower extremity function. The scores on Physical function scale of the SF-36 in total mITT population improved over the course of the study (mean increase in scores was 5.6 ± 9.44 points at Week 24) with slightly better improvements in the C-DM cohort than in the C-HT cohort (6.9 ± 9.21 vs. 4.1 ± 9.73).

Biochemical Measures (Thrombin-antithrombin, E-selectin, Adiponectin)
No trends were observed in the data for TAT. Mean E-selectin levels were higher among C-DM subjects compared to C-HT subjects; mean E-selectin levels decreased in C-DM subjects. Adiponectin levels at baseline were similar among subjects in the C-DM and C-HT cohorts; levels increased in both C-DM and C-HT groups, but there was a greater increase in the C-HT group.

Efficacy Outcomes in Study 415
Physician and subjects were asked to score the clinical status and severity of Cushing's syndrome by answering the set of questions every 3 months and comparing the severity of the disease at each visit to the severity of the disease at baseline and at previous visit. As per Sponsor, the severity of the disease as rated by physicians and by subjects improved: the physician's scores decreased from 4.4 at baseline to 3.4 at the last visit and the subject's scores decreased from 5.7 at study entry to 4.7 at last study visit (on a scale of 9=incapacitating to 1=absent). Of note, the instruments used are not validated for Cushing's syndrome complicating the conclusion further, even though the Sponsor specified that the instruments follow the generally accepted pattern of similar global assessment often used in clinical studies.

6.1.7 Subpopulations

The Sponsor stated that because of the sample size, no formal statistical analyses of treatment effect by age, and sex was performed. However, the Sponsor provided the summary tables for primary and key secondary endpoints by sex and age. Overall, the results of these analyses were not meaningful because of the small sample sizes. The summary of findings is presented below.

Age
Seventeen patients in C-DM cohort were ≤ 46 y.o and 8 patients were >46 y.o. The majority of patients in both age subgroup were responders and had at least 25 % reduction from baseline in $AUC_{glucose}$ at Week 24 visit: 11/17 patients (61%) who were younger than 46 years old, and 4/8 (57%) patients who were older than 46 years. In C-HT cohort, 15 patients were ≤ 50 y.o and 8 patients were >50 y.o. More older than younger subjects were responders and had at least 5 mm Hg reduction in DBP at Week 24: 3/6 (50%) subjects and 5/15 (33%) subjects, respectively. More subjects in C-DM cohort who were younger than 48 years had overall clinical improvement (score +1) at any visit as compared to the proportion of older patients who had clinical improvement at any visit: 16/31 (51.6%) subjects and 7/15 (46.7%) subjects, respectively. In C-HT cohort less older subjects than younger subjects had improvement in clinical scores of +1 at any visit: 10/31 (32.3%) subjects and 7/15 (46.7%) subjects, respectively.

Overall, the subgroups were small, thus, the interpretation of findings is complicated.

Gender
Of 25 patients enrolled in C-DM cohort, 6 patients were male and 19 patients were females. All males responded to treatment with Korlym by decreasing $AUC_{glucose}$ by 25% or more from baseline at the end of the study. Fewer females responded to the treatment: 9/19 (47.4%) were responders and had a reduction in $AUC_{glucose}$ by at least 25% at the end of the study. The preponderance of female subjects in C-DM cohort precludes meaningful interpretation of the findings. Of 21 patients enrolled in C-HT cohort, 8 were males and 13 were females. More males than females responded to Korlym treatment and had at least 5 mm Hg reduction in DBP at Week 24: 4/8 (50%) and 4/13 (30.8%), respectively. Overall clinical status improved in 18/32 (56.3%) females and in 5/14 (35.7%) males in C-DM cohort, and in 6/14 (42.9%) males and 11/32 (34%) females in C-HT cohort.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Sponsor conducted an exploratory analysis to evaluate the relationship between Korlym concentration and change in the key secondary endpoint. Ctrough of Korlym at the first visit at which a patient was declared a responder was evaluated. The Sponsor stated that the mean C_{trough} of Korlym at the occurrence of response was 1968.7 ng/mL which occurs in the 600 to 900 mg C_{trough} range. Based on these analyses, the Sponsor recommended starting dose of 300 mg once daily, the dose may be increased to 600 mg once daily based on the assessments of tolerability and clinical response.

Medical Officer's comments:
Additionally, as discussed in Section 7.2.1.2, the average dose in patients in C-DM cohort in Study 400 was 585 mg as compared to the patients in C-HT (723 mg) who were more most likely more resistant to the treatment with Korlym, and, thus, were on higher doses for the longer time with less obvious clinical benefit from the treatment. The requirement for the higher doses and longer treatment duration might be due to the overall resistance of BP control to the treatment with Korlym or to the overall less evident clinical improvement at doses higher than 600-900 mg.
This reviewer also analyzed the Korlym doses at Week 24/ET visit:

- *the majority of the responders in C-DM cohort were on 600 mg of Korlym at Week 24/ET visit (7 /15 subjects, 47%) followed by 1200 mg dose (5/15 subjects, 33%);*
- *the majority of responders in C-HT population were on 1200 mg of Korlym (4/8 patients) followed by 600 mg dose (2/8 patients, 25%).*

These findings may be indicative of the fact that the majority of the patients responded to doses of 600 mg, while only few more resistant patients respond to the dose of 1200 mg. The final conclusion can not be drawn at this time due to the small number of patients and wide and frequent dose fluctuations.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Sponsor stated that Study 400 was not designed to evaluate the development of tolerance to Korlym with prolonged treatment. Protocol-specified dose escalation occurred up to 1200 mg per day (900 mg for those weighing < 60 kg) based on tolerability and efficacy of the drug as judged by investigator. Most subjects achieved their maximum dose after the Week 10 visit.

Medical Officer's comments:
The glycemic control, weight reduction and improvement in overall clinical status in patients with Cushing's syndrome persisted during 6 months of the treatment with Korlym in Study 400 (refer to sections 6.1.4 and 6.1.5). The evaluation of the long-term persistence of the efficacy of the drug in patients with Cushing's disease would be desirable. An "escape" phenomenon may occur occasionally in patients with Cushing's disease who are treated with steroidogenesis inhibitors (except with ketoconazole) (Nieman, 2002)). This phenomenon is due to the reduced negative feedback by glucocorticoid receptor blockade, and may increase ACTH more. Elevated ACTH levels may stimulate further cortisol secretion. Eventually, very high cortisol levels may overcome glucocorticoid receptor blockade and lead to the loss of initial control of the disease. Unfortunately, no efficacy was evaluated in Study 415; although 27 patients continue to participate in the Study 415, thus, presumably, receive benefit from the treatment with Korlym. Additionally, fewer patients in Study 415 are on antidiabetic medications (37% of patients) as compared to 65% of patients in Study 400 who were on antidiabetic medications at baseline. This fact may be also indicative of the persistent efficacy of Korlym in glycemic control over the time; although only 17of 29 subjects previously enrolled in C-DM cohort in Study 400 participated in Study 415. Lastly, less fluctuation in doses is observed in patients participated in the Study 415, the majority of these patients continue treatment with fixed dose of Korlym, indicating that the desired efficacy and safety has been achieved and no further dose adjustments are required.

The review of published literature did not reveal obvious cases of the diminished efficacy of Korlym in patients with Cushing's syndrome due to the "escape" phenomenon; patients were treated with Korlym for up to 24 month. Of note, the majority of the reported patients were patients with ectopic ACTH- producing tumors. The occurrence of such phenomenon is unlikely in patients with ectopic ACTH producing tumors due to the autonomous ACTH production form such tumors that does not respond to the high cortisol levels.

6.1.10 Additional Efficacy Issues/Analyses

Supportive evidence for the efficacy of Korlym in patients with Cushing's syndrome is provided by a review of published literature. The individual reports are discussed in Section 9.1; this section will only briefly summarize the efficacy findings in published reports. Overall, 51 cases have been reported in the literature. Of these, seven subjects (5 subjects with Cushing's disease and 2 subjects with non-pituitary Cushing's syndrome) were included in short term pharmacodynamics study. The other 44/50 subjects with Cushing's syndrome were treated with

therapeutic courses of mifepristone 200-2000 mg/day (5-30 mg/kg) for up to 24 months. Mifepristone dose was frequently adjusted to increase efficacy or prevent adverse events.

Demographic characteristics of patients with Cushing's syndrome included in publications (Table 34)

All but two patients were adults (age 20-64 years); two pediatric patients (age 27 month and 13 years) were also presented. The majority of patients were females; gender was not reported in five patients. Twenty of 44 patients had ACTH-dependent Cushing's syndrome caused by ectopic ACTH-producing tumors in most of cases (14 patients). Nineteen patients had ACTH-independent Cushing's syndrome caused by adrenal carcinoma in most cases (17 patients). The source of Cushing's syndrome was not specified in five patients. Most of the patients have failed other treatment modalities in past including surgery, chemotherapy and other adrenolytic drugs.

Table 34. Demographics and Disease characteristics in Patients Included in Published Reports of Mifepristone for the Treatment of Cushing's syndrome

Demographic characteristics	No. of Patients (N=44)
Gender	
Male	14 (31.8%)
Female	25 (56.8%)
Not recorded	5 (11.4%)
Age Group	
Child (27 months)	1 (2.3%)
Adolescent (13 years)	1 (2.3%)
Adults (20 to 64 years)	41 (93.2%)
Age not specified	1 (2.3%)
Type of Cushing's Syndrome	20 (45.4%)
ACTH-Dependent Cushing's	
Cushing's Disease	5 (11.4%)
Ectopic ACTH	14 (31.8%)
Carcinoid	3 (6.8%)
Other	6(13.6%)
Not specified	5 (11.4%)
ACTH-dependent, source unknown	1 (2.3%)
ACTH-Independent Cushing's	19 (43.2%)
Adrenal carcinoma	17 (38.6%)
Adrenal adenoma	1 (2.3%)
Adrenal hyperplasia	1 (2.3%)
Unspecified Cushing's Syndrome	5 (11.4%)

Source: Sponsor's table 1, Module 5, Vol 39, module 5, Literature review, p. 6.

Efficacy of mifepristone in patients with Cushing's syndrome

Improvements in the clinical manifestations of Cushing's syndrome were reported in all but one report. A majority of patients had improvements in Cushingoid appearance including buffalo hump, moon facies, striae, edema, obesity and resolution of psychiatric symptoms. Twelve of reported patients had improvement in blood glucose levels and had reduction in the doses and/or

number of antidiabetic medications (one patient was concomitantly treated with metyrapone) (1-5, 7, 10) and eight patients had normalization of blood pressure (1,5,9,10). Of note, the total number of patients with diabetes or impaired glucose tolerance and or hypertension at the beginning of the treatment with mifepristone is not reported. Other improvements such as normalization of gonadal and thyroid hormone levels, reversal of heart failure, improved libido, muscular weakness, bruising and hypertrichosis were also reported in the literature. Efficacy findings are summarized in Table 35.

Table 35. Efficacy Observations during Mifepristone Treatment of Cushing's syndrome

Reference	N of patients reported	Age / sex	Etiology of CS	Efficacy findings	Dose of mifepristone
Beaufrere et al, 1987	1	27 mths		Weight loss Reduction of blood pressure and glucose to normal level Plasma and urinary cortisol and ACTH levels decreased	25 mg three times a day (5 mg/kg)
Bilgin et al, 2007	1	46 y/ F		Normalization of ACTH and cortisol levels and metabolic disorders Psychosis resolved Mifepristone co-administered with etomidate	
Cassier et al, 2008	2	46 y/ F	ECS *	**Case 1** Improvement of diabetes mellitus and facial and truncal swelling within 3 months Symptoms returned after 10 months of therapy and, except for glycemic control, did not respond to increased mifepristone doses	
		37 y/ F	ECS	**Case 2** Facial swelling, muscular weakness, hypertrichosis, and skin hematomas improved within 3 months Fasting blood glucose and HbA_{1C} normalized Hypertension and hypokaliema continued	
Castinetti et al, 2009	4		CD	Rapid improvement of clinical signs observed in 3/4 patients Psychiatric symptoms improved in 1/1 patients within the first week Increases in ACTH and cortisol in all patients	Median starting dose : 600 mg/day (300-600 mg) Median maximal dose: 700 mg/day (600-1200 mg)
	3		ECS[2]	Improvement of clinical signs observed in all patients Psychiatric symptoms improved in 1 patient within first week Insulin doses decreased or switched to oral anti-diabetic drugs with good glucose control (2/2 patients)	Median starting dose : 400 mg/day (400-600 mg) Median maximal dose: 600 mg/day (600-800 mg)
	12		ACTH	Rapid improvement of clinical signs observed in	Median

			independent CS	8/12 patients within first month Blood pressure decreased in 4/7 hypertensive patients Psychiatric symptoms improved in 1/2 patients within the first week Switch from insulin to oral anti-diabetic drugs in 1/4 patients with diabetes	starting dose : 400 mg/day (200-1000 mg) Median maximal dose: 600 mg/day (400-2000 mg)
	1		Adrenal hyperplasia	Improvement of clinical signs during first 3 months Metformin therapy stopped after 1 month; HbAlC levels improved after 6 months	600 mg/day
Chrousos et al, 1989	7**		ECS	Cushingoid phenotype normalized Depression ameliorated Hypertension decreased Carbohydrate intolerance eliminated Gonadal and thyroid hormone suppression corrected	5-22 mg/kg/day
	4		Unspecified	No efficacy data presented	
Chu et al, 2001	1	51 y/ M	CD	Clinical symptoms improved Discontinuation of antidiabetic meds Significant reversal of heart failure Resolution of psychotic depression Eventual normalization of adrenal axis as result of radiation treatment	400-1200 mg/day (6 mg/kg/day-25 mg/kg/day)
Contreras et al, 1987	1		Adrenal cancer	Clinical symptoms improved Metastatic tumor regression	20-30 mg/kg/day
Donckier et al, 1989	1	62 y/ M	Adrenal cancer	Beneficial effects on hypokaliemic alkalosis and DM	400 mg/day
Newfield et al, 2001	1	13 y/ F	Unspecified	Striae, weight gain, and buffalo hump improved.	400 mg/day
Nieman et al, 1985	1^	25 y/ M	EAS	Somatic features of Cushing's syndrome (buffalo hump, central obesity, and moon facies) ameliorated Mean arterial blood pressure normalized Suicidal depression resolved Libido returned Normalization of fasting and OGTT glucose levels	5-20 mg/kg/day
Nieman et al, 1987	1	30 y/ M	EAS	Facial plethora, moon face, truncal obesity, and peripheral edema resolved Blood pressure and serum potassium levels normalized Oral candidiasis resolved Improved glucose tolerance LH, total and free testosterone, plasma and urinary cortisol normalized	5-20 mg/kg/day
Oosterhuis et al, 2007	2	62 y /F, 57 y/ F	EAS	No efficacy data is presented	

Van der Lely, 1991	2	43 y /M, 32 y/ F	Adrenal cancer	Psychiatric symptoms improved within 12-24 hours All mental abnormalities disappeared within 24 hours-3 days Other signs and symptoms of Cushing's syndrome started to subside Plasma cortisol levels unchanged	400-800 mg/day

Source: Sponsor's table 3, Module 5, Vol 39, p. 9, modified
Improvement in glycemic control in red font; Improvement in BP control in blue font; Concomitant antiglucocorticoid mediations are highlighted in yellow
[1]This patient had decreased cortisol and ACTH to normal during the treatment, the levels remained normal after treatment discontinuation. Thus, improvement in clinical symptoms may be due to the resolution of hypercortisolemia, and not to the effect of mifepristone.
*Ectopic Cushing's syndrome
[2] One patient was concomitantly treated with metyrapone
** Includes data for one patient with adrenal carcinoma and one patient with adrenal adenoma (efficacy data not reported separately for these patients).
^ This patient also included in Chrousos et al (5) report.

Conclusion
Based on the published reports, mifepristone reduces clinical impact of hypercortisolemia and improves metabolic, psychiatric and somatic abnormalities associated with Cushing's syndrome. Additionally, mifepristone was demonstrated to be effective in patients with ectopic ACTH-secreting tumors and with ACTH-independent Cushing's syndrome as these Cushing's syndrome etiologies were the most represented in the published reports as compared to the patient population enrolled in Studies 400 and 415 (the majority of patients had Cushing's disease in these studies).

7 Review of Safety

Safety Summary

7.1 Methods

The primary safety data in support of the proposed indication of Korlym in patients with Cushing's syndrome is derived from the pivotal Study 400 and from extension Study 415 that provides supportive long-term safety data. Additional supportive evidence for the safety of Korlym is obtained from 27 studies conducted by Corcept in the other indications and in healthy volunteers. These studies include 12 studies in healthy subjects, 2 studies in subjects with renal or hepatic impairment, 9 studies in subjects with major depressive disorder with psychotic features, 3 studies in subjects with antipsychotic medication- induced weight gain, and one study in subjects with Alzheimer's disease. The 120-day safety update report and safety data from published literature of patients with CS treated with mifepristone are also reviewed in this section.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Refer to sections 5.1 and 5.2.

7.1.2 Categorization of Adverse Events

An AE was considered treatment emergent (TEAE) if it occurred after the administration of the first dose of the study drug. If the event occurred prior to the study enrollment, but worsened during study treatment it was also considered treatment emergent. Adverse events occurring ≤ 14 days after the last dose of study drug were also classified as treatment emergent. Serious adverse events were counted if they occurred within 30 days following cessation of treatment. Adverse events were coded using MedDRA version 10.0.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data from studies 400 and 415 were not pooled for the analysis because of the different study durations and designs. During pre-NDA meeting between Corcept and FDA (September 14, 2010), it was agreed that no Integrated Summary of Safety will be required for the submission and no pooling of safety data will be performed. Other Corcept-sponsored studies provided supportive safety data only; the data from these studies was not pooled for the analysis as well because of the different study designs, doses of Korlym used and duration of the treatment and different studied populations.

7.2 Adequacy of Safety Assessments

Overall, a total of 1349 subjects, including 50 subjects with Cushing's syndrome, were exposed to mifepristone in 29 Corcept-sponsored studies of mifepristone. The longest exposure to Korlym was in studies of Cushing's syndrome (Study 400 and 415). A total of 50 patients with Cushing's syndrome received 300 mg - 1200 mg of mifepristone treatment courses (up to 24 weeks) in the Study 400; of these, 30 patients received treatment with Korlym for up to 28 months in both studies 400 and 415 (as of cutoff date of May 27, 2011 for Study 415).

The safety data from the Korlym studies included in the clinical program was based upon standard safety endpoints, including adverse events, physical examination findings, clinical laboratory evaluation, and vital signs. Additional safety endpoints that have been incorporated into the study included transvaginal ultrasound with endometrial biopsies, MRI of pituitary, and ophthalmological evaluation.

Potential class effects on development of rash, vaginal bleeding were adequately assessed by the Sponsor. Additionally, the Sponsor conducted TQT Study, rash-rechallenge study and study evaluating effect of mifepristone on HDL-cholesterol.

The Korlym clinical experience regarding the extent and duration of the exposure needed to assess the safety of the drug is adequate.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.1.2 Demographics

Demographics of Target Population (Studies 400 and 415)
Demographic characteristics of 50 patients with Cushing's syndrome enrolled in Study 400 are discussed in Section 6.1.2. Of these, 30 patients (27 patients with Cushing's disease and 3 patients with ectopic ACTH-producing tumors) entered extension Study 415 and continued treatment with Korlym. Because, the Study 415 was an extension of Study 400, the demographic characteristics of patients enrolled in both studies were the same. The mean age of patients was 45 years in both studies; most of the subjects were white females (70 % and 65% in studies 400 and 415, respectively). Demographic characteristics of the subjects who participated in the both studies (400 and 415) are presented in Table 36.

Table 36. Demographic Characteristics in the Primary and Extension Studies (Study 400 and 415)

Demographic characteristics	Study 400	Study 415
Sex, n (%)	M: 15 (30.0) F: 35 (70.0)	M: 10 (33.0) F: 20 (66.7)
Age (years)	Mean(SD): 45.4 (11.85) Range: 26-71	Mean (SD): 46.1 (11.74) Range: 27-71

Source: Sponsor's table 3, p. 9, 4-month Safety update, module 2, vol 1

Demographics of patients enrolled in the other Corcept-sponsored studies
The majority of the subjects enrolled in the other supportive studies were middle age subjects 40-50 years old; the mean age varied from 24.7 ± 5.43 y.o in patients participating in TQT Study to 76.1 ± 7 y.o in patients with Althheimer's disease. Male-to-female ratio also varied substantially among the patients enrolled in these studies with 100% females being enrolled in HDL study to 100 % males being enrolled in TQT Study and prevention of weigh gain study.

7.2.1.2 Exposure

Study 400
Fifty subjects in Study 400 received at least one dose of Korlym. All patients received 300 mg of Korlym daily as an initial dose; the dose was escalated at 2-4 weeks intervals based on clinical response and adverse event profile to a maximum 1200 mg. Doses was reduced at the discretion of Investigator. The mean duration of the exposure to study drug was 133.3 days (median 166 days). Mean exposure was longer in the C-HT cohort (138.6 days) as compared to the exposure in C-DM cohort (129.5 days). The mean daily dose of Korlym was also higher in C-HT cohort as compared to C-DM cohort (723.9 mg and 585.4 mg, respectively). The mean number of days of higher dosing with Korlym (at the 900 mg and 1200 mg doses) was also longer in C-HT cohort

than in C-DM cohort. In contrast, the mean number of days of dosing at 300 mg and 600 mg doses was longer in the C-DM cohort than in the C-HT cohort (Table 37).

Table 37. Extent of Exposure in Study 400 (ITT/Safety Population)

	C-DM (N=29)	C-HT (N=21)	Overall (N=50)
Total duration of exposure (days)			
n	29	21	50
Mean (SD)	129.5 (60.434)	138.6 (45.448)	133.3 (54.320)
Median	167.0	166.0	166.0
Min, Max	14.0, 179.0	34.0, 172.0	14.0, 179.0
Average daily dose (mg)			
n	29	21	50
Mean (SD)	585.4 (268.21)	723.9 (233.48)	643.6 (261.00)
Median	603.5	795.7	675.6
Min, Max	50.0, 1022.0	300.0, 987.2	50.0, 1022.0
Number of days at 300 mg (days)			
n	29	21	50
Mean (SD)	31.0 (25.273)	22.76 (24.073)	27.60 (24.876)
Median	15.0	15.0	15.0
Min, Max	4.0, 94.0	13.0, 122.0	4.0, 122.0
Number of days at 600 mg (days)			
n	24	21	45
Mean (SD)	53.92 (41.544)	35.57 (21.885)	45.36 (34.721)
Median	36.5	28.0	29.0
Min, Max	12.0, 164.0	18.0, 124.0	12.0, 164.0
Number of days at 900 mg (days)			
n	18	16	34
Mean (SD)	29.89 (33.090)	42.44 (33.627)	41.09 (32.859)
Median	28.0	28.5	28.0
Min, Max	8.0, 127.0	13.0, 119.0	8.0, 127.0
Number of days at 1200 mg (days) n	10	12	22
Mean (SD)	65.00 (41.836)	72.17 (32.476)	68.91 (36.275)
Median	74.0	83.5	83.5
Min, Max	6.0, 112.0	14.0, 103.0	6.0, 112.0

Source: Sponsor's table 28, Module 5, Vol 31, CSR 400, p. 103.

Medical officer's comments:
Overall, higher doses and longer duration of treatment with higher doses of Korlym were required by patients in C-HT cohort to achieve treatment goals (control of hypertension, in particular) as compared to the doses used in patients in C-DM cohort. The requirement for

the higher doses and longer treatment duration might be due to the overall resistance of BP control to the treatment with Korlym.

Study 415
Based on the visits completed by subjects in the extension Study 415 as of the cutoff date of May 27, 2011, cumulative duration of exposure in both studies (400 and 415) was as follows: 4 patients had more than 6 months but less than 12 months of exposure and 24 subjects had at least 12 months of exposure (Table 38). The cumulative exposure from the two studies does not include the 6-Week period between the two studies when no treatment was administered.

Table 38. Extent of Cumulative Exposure (Study 400 and 415)

Duration of exposure (months)	N=30
< 12 months	4 (13%)
12 months	3 (10%)
13 months	2 (7%)
15 months	1 (3%)
16 months	4 (13%)
18 months	1 (3%)
19 months	2 (6%)
20 months	1 (3%)
21 months	1 (3%)
22 months	3 (10%)
23 months	1 (3%)
24 months	3 (10%)
26 months	1 (3%)
27 months	3 (10%)
28 months	1 (3%)

In Study 415, 24/30 subjects received treatment with stable doses of Korlym. The majority of patients received 600 mg of Korlym daily (8/30, 27% of patients) or 1200 mg of Korlym (10/30, 33% of subjects) daily. Three subjects (10%) received doses of 300 mg daily and three subjects (30%) received doses of 900 mg daily. Doses of Korlym varied in 6/30 subjects during the study (minimum dose -300 mg, maximum dose 1800 mg). Two subjects received doses of Korlym of 1800 mg; these doses were allowed at the request of the Investigator. Both subjects had ectopic ACTH-producing tumors and very high ACTH and cortisol levels. These doses were subsequently reduced to 1200 mg once a day.

Exposure to the study drug in non-Cushing's Corcept-sponsored studies
The longest duration of the exposure to mifepristone was in patients with Alzheimer's disease who received 300 mg of mifepristone for 16 weeks. All other studies were single dose studies (PK studies) or studies of short duration (7-28 days); patients received 300 -1200 mg of mifepristone in these studies (refer to Section 5.3.3).

7.2.2 Explorations for Dose Response

The Sponsor investigated the frequency of TEAEs per each dose level in Study 400 (Table 39). Overall, no conclusion regarding the relationship between dose and frequency of TEAEs including SAEs could be drawn: the doses and duration of the treatment with each dose varied in individual patients, the dose could have been increased or decreased during the study, and only few patients were on stable doses during the study. Moreover the overall patient population enrolled in the study was small, the number of patients per each dose level group was unbalanced and the number of AEs by system organ class (SOC) and preferred term (PT) was too small, complicating the interpretation of the findings even more. The higher incidence of TEAEs in Study 400 occurred at dose levels $\geq$ 300 mg - < 600 mg and $\geq$ 600 mg - < 900 mg (82% and 80%, respectively) than at dose levels < 300 mg and $\geq$ 900 mg (14% and 64%, respectively). The decreased frequency of AE at the highest dose levels ($\geq$ 900 mg) may be due to the fact that only few patients were on stable highest doses of Korlym, the duration of treatment with the highest doses was shorter and the Investigators usually decreased the dose once the TEAEs developed. The majority of patients who developed fatigue, nausea, vomiting and headache received doses of 300-600 mg of Korlym (14, 13, 6 and 13 patients respectively). No fatigue was observed at dose level $\geq$ 600 mg. Hypokalemia and thyroid function abnormalities occurred more frequently in patients who received higher doses of Korlym, > 900 mg, most likely because of imbalanced number of patients per dose level and/or longer duration of the exposure.

In Study 415 no dose-dependency for the development of the drug related AE was noted as well; the overall incidence of events was generally lower in the extension Study and adverse events profile was similar as compared to the incidence and profile of AEs reported in Study 400. Additionally, patient population enrolled in the study and the number of AE by SOC and PT was too small to allow any further exploratory analysis.

Table 39. Summary of TEAEs by Dose Levels in Safety population (Study 400)

System Organ Class/ Preferred Term	Dose level, n of patients (%)			
Total 50 patients	**< 300 mg**	**≥ 300 - < 600mg**	**≥600-<900 mg**	**≥ 900 mg**
Number (%) of Subjects with at least 1 TEAE	7 (14)	41 (82)	40 (80)	32 (64)
Gastrointestinal disorders				
Nausea	1 (2)	13 (26)	6 (12)	10 (20)
Vomiting	1 (2)	6 (12)	2 (4)	6 (12)
Dry mouth	1 (2)	5 (10)	2 (4)	4 (8)
Diarrhea		4(8)	3 (6)	1 (2)
Constipation		1 (2)	4 (8)	
Gastroesophageal reflux disease	1 (2)		2 (4)	1 (2)
Abdominal pain			1 (2)	2 (4)
General disorders/ administration site conditions				
Fatigue	1 (2)	14 (28)		9 (18)
Edema peripheral	1 (2)	5 (10)	5 (10)	6 (12)
Pain		3 (6)	3 (6)	2 (4)
Asthenia	1 (2)	2 (4)		2 (4)
Malaise		2 (4)	1 (2)	
Edema		2 (4)		2 (4)
Pitting edema			2 (4)	1 (2)
Thirst			1 (2)	
Chest discomfort			2 (4)	1 (2)
Nervous system disorders				
Headache		13 (26)	9(18)	7 (14)
Dizziness	1 (2)	4 (8)	6 (12)	5 (10)
Somnolence		1 (2)	1 (2)	4 (8)
Musculoskeletal and connective tissue disorder				
Arthralgia		5 (10)	3 (6)	8 (16)
Back pain		5 (10)	4 (8)	
Myalgia		3 (6)	3 (6)	3 (6)
Pain in extremity		2 (4)	1 (2)	3 (6)
Muscular weakness		2 (4)		2 (4)
Flank pain		1 (2)		2 (4)
Musculoskeletal chest pain			1 (2)	2 (4)
Musculoskeletal stiffness		1 (2)	1 (2)	1 (2)
Rheumatoid arthritis				
Investigations				
Blood potassium decreased	1 (2)	4 (8)	7 (14)	8 (16)
Thyroid function test abnormal		1 (2)	1 (2)	7 (14)
Blood triglycerides increased		1 (2)		3 (6)
Skin and subcutaneous tissue disorders				
Dry skin	1 (2)		2 (4)	
Ecchymosis	1 (2)	1 (2)		
Acne		2 (4)	1 (2)	
Infections and Infestations				
Sinusitis	2 (4)	2 (4)	2 (4)	2 (4)

Nasopharyngitis	1 (2)	1 (2)	3 (6)	3 (6)
Urinary tract infection		1 (2)	1 (2)	2 (4)
Upper respiratory tract infection			2 (4)	1 (2)
Endocrine disorders				
Cushing's syndrome		2 (4)		2 (4)
Eye disorders				
Vision blurred		1 (2)		3 (6)
Metabolism and nutrition disorders				
Decreased appetite		3 (6)	3 (6)	
Anorexia	2 (4)	3(6)	1 (2)	
Hypoglycemia			2 (4)	
Vascular disorders				
Hypertension		3(6)	5 (10)	5 (10)
Hot flush		1 (2)	1 (2)	1 (2)
Reproductive system and breast disorders				
Endometrial hypertrophy		1 (2)	2 (4)	7 (14)
Vaginal hemorrhage		1 (2)	1 (2)	2 (4)
Metrorrhagia		1 (2)	1 (2)	1 (2)
Psychiatric disorders				
Anxiety		2 (4)	2 (4)	3 (6)
Insomnia		1 (2)	1 (2)	1 (2)
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	1 (2)		4 (8)	3 (6)
Cough			1 (2)	
Pharyngolaryngeal pain		1 (2)	3 (6)	

Source: Sponsor's table 14.3.1.9.2 , Module 5, Vol 32

7.2.3 Special Animal and/or In Vitro Testing

Refer to Dr. Patricia Brundage's review for details.

Briefly, chronic toxicity studies conducted in rats and mice demonstrated ophthalmologic findings of retinal atrophy, pharmacologic effects on reproductive organs, and an increase in thyroid and liver neoplasms. The reproductive changes were consistent with the known pharmacology of mifepristone as progesterone and glucocorticoid receptor antagonist. There was no retinal atrophy demonstrated in dogs or humans up-to-date. The liver and thyroid neoplasms occur in the rat studies only. However, Pharm. Tox reviewer concluded that the relevance of the liver and thyroid tumors observed in rats to humans is equivocal and cannot be excluded. The signs of hepatocellular toxicity were also noted in dog and mouse. Based on this animal data, Pharm. Tox reviewer recommended periodic monitoring of liver transaminases levels in patients exposed to mifepristone for a chronic duration. The only clinically relevant animal findings were: a significant inhibitory effect of parent compound and its metabolites on hERG potassium current and dose-related prolongation of the QT and QTc-intervals in the chronic toxicity dog study. Additionally, *ex vivo* and *in vitro* studies predict that mifepristone may induce the metabolism of drugs that are substrates for the CYP3A and CYP2B enzymes.

7.2.4 Routine Clinical Testing

The clinical testing performed routinely in all studies was adequate overall to elicit AEs and other clinical and laboratory parameters that could represent a safety concern. EKG was performed at prespecified endpoints in both studies in Cushing's syndrome and occasionally was monitored in the other Corcept-sponsored studies to assess potential QT interval prolongation. Additionally, three special safety studies were conducted by Corcept to evaluate the effect of mifepristone on QT interval (Study 300), effect of mifepristone on HDL cholesterol levels (Study 425) and rechallenge study to evaluate the reoccurrence of the rash (Study 301).

7.2.5 Metabolic, Clearance, and Interaction Workup

The Sponsor's testing of Korlym's metabolism, clearance and potential for interaction has already been discussed in Section 4.4.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no other glucocorticoid receptor blockers currently available.

The potential adverse events that are related to the antiglucocorticoid and antiprogesterone action of Korlym, including adrenal insufficiency, hypokalemia and endometrial hypertrophy, are discussed in Section 7.3.5.

7.3 Major Safety Results

7.3.1 Deaths

Studies in Cushing's syndrome (Study 400 and 415)
There were five deaths in both studies: four deaths in Study 400 and one death in Study 415. All deaths were unrelated to the study drug. The deaths recorded in Study 400 occurred in subjects with metastatic adenocarcinoma (3 subjects) and neuroendocrine cancer (1 subject) due to the progression of the disease. One subject in Study 415 died of amyloidosis. The narratives of the subjects who died during the studies are provided below:

Study 400
1. Subject #07-003 (C-DM) a 33-year-old female with Cushing's syndrome due to metastatic adrenal cortical carcinoma received the first dose of Korlym on December 03, 2008. Her medical history was significant for liver resection, tumor resection, cholelithiasis, diarrhea, hypertension, tachycardia, glucose intolerance, hypothyroidism, obesity, amenorrhea, anxiety, depression, and shortness of breath. She received multiple concomitant medications during the study including antihypertensive, antipsychotic and narcotic medications, mitotane, potassium, and spirinolactone. (b) (6), the subject was admitted to the hospital with abdominal pain and was diagnosed with a progression of her underlying adrenal carcinoma. Because of overall poor prognosis, the subject discontinued study drug on February 09, 2009. She received

total of 9 weeks of Korlym treatment; the last dose was 1200 mg. She died from adrenal carcinoma (b) (6).

2. Subject #07-006 (C-HT) a 48-year-old male with Cushing's syndrome caused by metastatic adrenal carcinoma received the first dose of the study drug on March 11, 2009. His medical history was significant for the tumor resection, status post-chemotherapy, palliative external beam radiation for the right flank pain due to the tumor invasion, intramedullar schwanoma, anemia, and hypertension. His concomitant medications included mitotane, narcotics, multiple antihypertensive medications, potassium, spironolactone and prednisone (not for adrenal insufficiency). He continued treatment with Korlym till June 30, 2009; his last dose of Korlym was 1200 mg. The subject died on (b) (6) from disease progression.

3. Subject #07-008 (C-DM) a 38-year-old female with Cushing's syndrome due to metastatic adrenal cortical carcinoma started treatment with Korlym on August 06, 2009. Her medical history was significant for thoracotomy, pulmonary metastases, hypertension, glucose intolerance, depression. Her concomitant medications included multiple antihypertensive medications, oxygen, potassium, spirinolactone, and mitotane. On September 16, 2009 (end of Week 6) nausea, headaches, and shortness of breath worsened and chest x-ray revealed large metastatic lesions in both lungs. Patient was taking 900 mg Korlym at that time. The subject was unable to return to the research site for further evaluations because of the disease progression. The subject continued taking Korlym until October 09, 2009 and died on (b) (6) from metastatic adrenocortical carcinoma.

4. Subject #20-002 (C-DM) a 66 year-old female with Cushing's syndrome due to ectopic ACTH secretion from a neuroendocrine carcinoma with abdominal metastases received first dose 300 mg of the study medication on July 28, 2009. Her medical history was significant for renal insufficiency, generalized abdominal pain, hypertension, diabetes mellitus, and asthma. Her concomitant medications included multiple antihypertensive medications and insulin. On August 12, 2009 she developed hypoglycemia, hypokaliema, and was successfully treated with glucose and potassium supplements. Because of the disease progression, the subject initiated chemotherapy with cisplatin, etoposide and dexamethasone on August 19, 2009. As a consequence of chemotherapy, the subject developed nausea, vomiting and hypoglycemia again (glucose levels were in the 50-60 mg/dL range). She continued taking study medication till the time of death. The subject died (b) (6) because of the disease progression.

Study 415

Patient # 06-003, 30-year old male with Cushing's disease completed Study 400 on March 2, 2010 (was in C-DM cohort) and was enrolled in Study 415 on March 2, 2010, but did not started the study drug (dose 300 mg) until March 8, 2010 because of hypokaliema. His medical history was significant for pituitary surgery, pituitary radiation, diabetes, hypertension, hyperlipidemia, osteoporosis and hypopituitarism. During the 6-Week follow-up visit in Study 400, patient was diagnosed with elevated alkaline phosphatase levels (515 U/l). Of note, patient had elevated alkaline phosphatase levels of 169 U/l (normal range < 125 U/l) during Week 16 visit in the Study 400. The follow-up labs on March 15, 2010 revealed further increase in AlkPhos level to

811 U/L; bilirubin was also elevated to 51.3 umol/L (normal range < 22 umol/L). ALT and AST levels remained within normal limits. Patient developed SAE of bacterial arthritis (b) (4), (b) (6) and was hospitalized; the event is described in Section 7.3.2. During hospitalization the levels of alkaline phosphatase and bilirubin increased further to 1500 U/l and 136.8 umol/L, respectively, thus, the study drug was discontinued on (b) (6). Liver CT scan and cholangiopancreatography were normal; liver biopsy revealed amyloidosis, and immunologic and hematologic tests and bone marrow aspiration revealed multiple myeloma. The Sponsor concluded that amyloidosis might be due to multiple myeloma. Patient's condition continued to deteriorate; he developed renal failure, hypotension and disseminated intravascular coagulation. Patient died (b) (4), (b) (6).

Medical Officer's comments:
This reviewer agrees with the conclusion that the all deaths on the study occurred most likely because of the disease progression in patients with metastatic malignant tumors.

Deaths in other Corcept-sponsored studies

No deaths occurred in PK studies in healthy volunteers and in Special population and in drug-drug interaction studies. Overall, 8 deaths occurred in other Corcept-sponsored studies, of these, four deaths occurred in patients who were treated with mifepristone. All deaths were unrelated to the study drug. The list of deaths is presented in Table 40.

Table 40. Listing of deaths in supportive Corcept's studies in other indications

Mifepristone			**Placebo**	
Subject Number	Event Preferred Term	Mifepristone Dose at Time of Event	Subject Number	Event PT
Studies in patients with major depression with psychotic features				
C1073-02[1]				
14-122	Congestive heart failure	600 mg	11-002	Hypertensive heart disease
			33-110	Hypertrophic cardiomyopathy
C1073-06[2]				
04-0683	Acute intoxication with multiple substances	300 mg		
26-0457	Drug toxicity	300 mg		
C1073-09[3]				
33-106	Completed suicide	600mg	34-024	Injury asphyxiation
Prevention of Weight Gain				
C1073-200-1 (olanzapine)			1055	Road traffic accident (head injury)

Source: Sponsor's table 17, Module 2, Vol 4, Summary of Clinical Safety (SCS), p. 68, modified;
Deaths in mifepristone group are highlighted.
[1-3] Refer to Medical Officer's comments below.

Medical Officer's comments:
1. The Sponsor stated that all deaths in Study C1073-02 were cardiac related and were considered not related to the study drug. No other information was provided in all cases including age, underlying disease and concomitant medications, thus, not allowing an assessment of the causal relationship with mifepristone.
2. Two patients died during Study C1073-06. One subject had an acute intoxication with multiple substances including opiates, fluoxetine, diphenhydramine, mirtazapine, olanzapine, zolpidem, quetiapine, and diazepam in 3 days after completing treatment with 300 mg mifepristone. The other subject had morphine intoxication approximately 2 weeks after completing treatment with 300 mg mifepristone. The overdose with multiple antipsychotic medications and narcotics is not unusual in patients who have underlying depression and are treated with multiple drug regimens; thus, fatal outcomes most likely were not related to Korlym use.
3. One patient treated with Korlym died in Study C1073-09 due to strangulation; suicide is not unusual event in patient with severe underlying depression with psychotic features, thus, this death is most likely not related to Korlym use.

7.3.2 Nonfatal Serious Adverse Events

Studies in Cushing's syndrome
Overall, 21 subjects experienced 39 nonfatal SAEs in both studies, 400 and 415: 13/50 (26%) subjects in Study 400 and 9/30 (30%) subjects in Study 415.

In Study 400, 13 subjects (26%) experienced 23 nonfatal SAEs: 7 patients were enrolled in C-HT cohort and 6 patients - in C-DM cohort. Seven events were considered by the Investigators as possibly or probably related to the study drug: orthostatic hypotension, respiratory failure, confusion, hypokalemia, vomiting, adrenal insufficiency and asthenia. In this reviewer's opinion, episode of asthenia in subject #08-014 was suspicious for the adrenal insufficiency (please refer to the patients' narratives), thus a total of two SAEs of adrenal insufficiency developed during the study. Three SAEs led to the treatment withdrawal: respiratory failure, cardiomyopathy and asthenia (refer to the Section 7.3.4*).* The relationship between dose level of Korlym and occurrence of the SAEs was analyzed, but no conclusion regarding a possible relation between the dose level and occurrence of the SAEs can be drawn since the number of SAEs was small. Overall, SAEs developed in 4 subjects receiving ≥ 900 mg (4 SAEs), in 7 subjects (8 SAEs) receiving ≥ 600 mg- < 900 mg, in 4 subjects (5 SAEs) receiving ≥ 300 mg- < 600 mg and in 2 subjects (2 SAEs) receiving < 300 mg of Korlym.

In Study 415, 9/ 30 subjects (30%) experienced 15 non-fatal SAEs. Only one SAE, hypokalemia, was drug-related (in patient #10-002). No SAEs led to the treatment withdrawal. Overall, no new trend in the type or frequency of the SAE was noticed in Study 415 as compared with Study 400. Overall, no new trend in the type or frequency of the SAEs was noticed in Study 415 as compared to Study 400.

<u>The narratives of the patients who developed SAEs in Study 400:</u>

1. Subject #06-003 (C-DM), a 67-year-old male with Cushing's disease developed four SAE: orthostatic hypotension, foot fracture, intracranial aneurism, and erosive gastritis. Orthostatic hypotension was considered as SAE possibly related to the study drug. Patient's medical history was significant for colostomy, conventional radiation, diabetes insipidus, heart ischemic changes, hypertension, hypothyroidism, DM, osteoporosis, erecti1e dysfunction, and depression. Patient was treated with multiple medications including multiple antihypertensive medications, desmopressin, levothyroxine, potassium. In 2 months after treatment initiation with Korlym (dose 600 mg), the subject began experiencing moderate dizziness that increased upon standing; BP was 106/70 mm HG. The Investigator determined that the subject had orthostatic hypotension and discontinued the treatment with metoprolol and furosemide. The dizziness continued; the subject fell several times. During one of these falls the subject fractured left foot. Patient was evaluated in emergency room, chemistry and CBC results were normal. Patient received one dose of 4 mg of dexamethasone i.v for treatment of possible adrenal insufficiency and Korlym was discontinued. The hypotension resolved and subject was restarted on Korlym 300 mg in 1 month. At Week 10 visit the subject was diagnosed with multiple intracranial aneurysms (largest 5 mm) by CT and MRI. Subject completed approximately 5.5 months of the study, and underwent surgery in 10 days after the last dose. In postoperative period subject was treated with clopidrogel and heparin and developed erosive gastritis (in 3 weeks after the last dose of Korlym); the event resolved.

Medical Officer Comments:
The conclusion regarding the association of orthostatic hypotension with study medication can not be drawn. This subject had multiple medical conditions that may cause abnormal intravascular tone regulation (diabetes), dehydration (diabetes insipidus), and was on multiple medications that may affect blood pressure control (b-blockers, diuretics, hydrocodone). Moreover, the hypotension did not resolve after dexamethasone administration. Other SAE were not drug related.

2. Subject #07-009, a 45-year-old female with Cushing's disease developed one SAE, respiratory failure that was considered as possibly related to the study drug; the event led to the study withdrawal. Medical history of this patient included CREST syndrome, scleroderma, mixed connective tissue disease, Reynaud's syndrome, pulmonary hypertension, sleep apnea and obesity. In 1 month after the initiation of treatment with Korlym subject developed severe respiratory failure with hypotension, was hospitalized and intubated; patient was on 600 mg of Korlym at time of the event. Patient was diagnosed with ARDS and received vasopressors, i.v hydration and glucocorticoids; Korlym was discontinued permanently upon admission. The event resolved. The event was considered possibly related to study drug because of the temporal association of respiratory insufficiency and the increase in Korlym dose from 300 mg to 600 mg daily.

Medical Officer's comment:
The event of respiratory failure was considered possibly related to study drug because of the temporal association of respiratory insufficiency and the dose change. The occurrence of respiratory insufficiency can not be explained by the mechanism of action of Korlym, and

there was no increase incidence of the respiratory insufficiency across the Corcept's clinical program. However, this patient had medical history of multiple autoimmune disorders and pulmonary hypertension. The high levels of circulating cortisol prior to the initiation of the study treatment may have masked the manifestations of the underlying autoimmune disorders including respiratory symptoms. Korlym prevents biological action of cortisol, thus, the study treatment may have exacerbated the manifestations of these autoimmune disorders and worsen the respiratory symptoms in patient with already compromised pulmonary vasculature.

3. Subject #07-010 a 26-year-old male with Cushing's disease had two SAEs, confusion and hypokalemia. Both events were rated as possibly drug related. Medical history of this subject included diabetes insipidus, diarrhea, numbness and weakness in left lower extremities, and depression. To control chronic pain the subject had been taking hydromorphone, oxycodone, morphine, lorazepam, and marijuana. In three weeks after initiation of the treatment with Korlym, subject became more confused and was admitted to the hospital; subject was taking 600 mg of Korlym at that time. The dose of oxycodone and lorazepam was decreased, hydromorphone was discontinued. His mental status improved. Treatment with Korlym was continued during the event. The event was considered possibly related to study drug because of the temporal association between the event's onset and the increase in dose of Korlym. Additionally, the possible drug-drug interaction between Korlym (inhibitor of CYP3A) and oxycodone and tetrahydrocannabinol was suspected; Korlym inhibits CYP3A4 isoenzyme and may decrease metabolism of oxycodone and tetrahydrocannabinol that is CYP3A-dependent. The second SAEs, severe hypokalemia (2.1 mEq/L) occurred in 4 months after the study onset (dose of Korlym was 1200 mg). Patient also had elevated blood pressure at the time of the event, 150/97 mm Hg; ECG showed sinus rhythm at 70 beats per minute, frequent PVCs, and possible U waves. He was hospitalized and, treated with potassium and spironolactone. The hypokaliema resolved. Korlym was not discontinued during the event.

Medical Officer's comments:
1.The conclusion regarding relationship between the study drug and worsening of the confusion can not be drawn. Although the drug-drug interaction can not be ruled out, the overdose with multiple narcotics even without concomitant use of Korlym may occur and cause the confusion. Moreover, the overdose with multiple narcotics is not unusual in patient with underlying depression who take multiple narcotic drugs for pain control.
2 .Symptomatic hypokalemia and concomitant hypertension was, most likely, caused by the activation of mineralocorticoid receptors by elevated cortisol levels secondary to Korlym treatment, thus this event was drug-related.

4. Subject #08-013 (C-DM) a 34-year-old female with Cushing's disease developed two SAE, vomiting (related to the study drug) and sinusitis (unrelated to the study drug).
Patient developed severe vomiting during acute sinusitis event in 2 months after initiation of the treatment with a study drug (the dose was 600 mg). Patient was hospitalized, the study drug was discontinued and patient was treated with antibiotics and prednisone. As per investigator, the glucocorticoids were given for treatment of acute sinusitis and not for the adrenal insufficiency.

Medical officer's comments:
The definite conclusion regarding relationship between the study drug and vomiting can not be drawn. Vomiting developed concomitantly with occurrence of sinusitis and headache, but improved after the initiation of the treatment of the sinusitis with glucocorticoids and antibiotics; patient was able to take these drugs orally. Thus the event of vomiting might be due to the acute infection/inflammation or to adrenal insufficiency (improved with glucocorticoid treatment).

5. Subject 08-014 (C-HT) a 61-year-old male with Cushing's disease developed two SAEs of asthenia during the study; the first episode was considered related to the study drug; the second episode was considered as unrelated to the study drug. Patient was treated with 900 mg of Korlym when he developed the first episode of vomiting, nausea and weakness at Week 10 visit. Korlym was discontinued and dexamethasone was administered for the possible adrenal insufficiency in tapering doses for 9 days; treatment resulted in the clinical improvement. Weakness, nausea and vomiting reoccurred in 2 days after dexamethasone discontinuation (the study drug has not been restarted yet). Patient was admitted to the hospital, and administered hydrocortisone 100 mg i.v followed by dexamethasone 2 mg twice a day for 9 days. Blood pressure was 123/80 mm Hg at the time of the event. The event resolved and was rated as SAE possibly related to the study drug. Korlym was restarted at 300 mg. The subject developed nausea and vomiting after the administration of the first dose of the study drug; thus, Korlym was permanently discontinued. Subject developed the second episode of asthenia and nausea in 16 days after Korlym disconsolation, and was hospitalized again (the second SAE); blood pressure was 160/108 mmHg at that time. No glucocorticoids were administered; patient was discharged from the hospital next day. Patient continued experienced weakness after bilateral adrenalectomy as well.

Medical Officer's comment:
The Sponsor defined both AEs as asthenia. In this reviewer's opinion, combination of vomiting, nausea and asthenia during the first episode of asthenia is suspicious for the development of adrenal insufficiency in this subject. Additionally, the symptoms improved after the dexamethasone administration and reoccurred after the dexamethasone discontinuation (refer to Section 7.3.5). The second episode of asthenia occurred after the drug was stopped, and may be due to the reoccurrence of hypercortisolemia associated with Cushing's syndrome.

6. Subject #22-001 (C-HT) a 50-year-old female with Cushing's disease developed an SAE of adrenal insufficiency that was drug-related. Patient developed weakness, nausea, vomiting and decreased appetite in 5 months after she was started on Korlym; the dose was 1200 mg at time of the event. Blood pressure was normal 141/75 mmHg. Patient had concomitant hypokalemia but no other electrolyte abnormalities. The subject was admitted to the hospital and treated with i.v. fluids, dexamethasone for 5 days and potassium; Korlym was discontinued. The event resolved. The study drug was resumed at dose 300 mg in Study 415.

7. Subject #01-003(C-HT), a 38-year-old woman with Cushing's disease developed Legionella pneumonia. The event was considered severe and not related to the study drug AE. Patient developed vomiting, shortness of breath, hypoxia, cough, fever, and diarrhea in 2 months after initiation of the treatment with the study drug (the dose was 900 mg). The study drug was discontinued and patient was treated with inhalers, dexamethasone and levofloxacin. Blood tests results were positive for Legionella (IgM titer was 1:256). Patient also had simultaneous elevation in LFT's during the event (ALT 138 U/l, AST 151 U/l). The Sponsor indicated that elevated liver enzymes were associated with concomitant viral syndrome. The treatment with Korlym 300 mg was restarted after the resolution of the event (in 1 month).

8. Subject #06-002 (C-HT), a 67-year-old male with ectopic ACTH- producing tumor developed severe chest pain while being treated with Korlym. The event was considered not related to the study drug. His medical history was significant for cardiac occlusion (50%), hypercholesterolemia, hypertension, left ventricular hypertrophy, mitral valve regurgitation, and rheumatoid arthritis. Patient has been on stable dose of Korlym 600 mg at time of the event. He was admitted to the hospital; vital signs, electrolytes, troponin, chest x-ray, ECG and stress test were normal. The event resolved within 1 day. The study drug was not interrupted.

9. Subject #07-004 (C-DM) a 48-year-old female with Cushing's disease developed three SAEs during the study: two episodes of dyspnea and one episode of respiratory failure. All events were considered unrelated to the study drug. Her significant medical history included deep vein thrombosis, pulmonary embolism, hypoxia, chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea; patient was also on chronic oxygen supplementation. Patient experienced two episodes of worsening of dyspnea and COPD during the study: in 5 days and in 1 month after initiation of the treatment with Korlym. Patient was hospitalized during both events; Korlym was interrupted for 10 days after the first episode of dyspnea. Of note, the subject was noncompliant with oxygen therapy. Patient had exacerbation of COPD again and developed acute respiratory failure later in the study. The drug was not interrupted, the event resolved.

10. Subject #08-001 (C-HT) a 44-year-old female with Cushing's disease had one SAE of migraine exacerbation during screening period that occurred and resolved prior the administration of the first dose of Korlym; it was considered unrelated to the study drug.

11. Subject #08-003 (C-DM) a 60-year old female with Cushing's disease had three SAEs: pulmonary edema, renal failure and worsening of cardiomyopathy. All events were considered unrelated to the study drug. The subject had worsening of pre-existing cardiomyopathy in 1.5 months after the initiation treatment with Korlym. The drug was discontinued because of the event. Two other events occurred after the study drug has been already discontinued: pulmonary edema and moderate renal insufficiency (serum creatinine 2 mg/dL) with "mildly elevated liver function tests" in 1 week and 1 month after the study drug discontinuation, respectively. All events resolved.

12. Subject #11-003 (C-DM) a 33-year-old male with Cushing's disease developed pulmonary embolism that was considered unrelated to study drug. This SAE occurred in 1.5 months after initiation treatment with Korlym, patient was admitted to the hospital. The event resolved.

Medical Officer's comment:
Cushing's syndrome is associated with hypercoagulable state; the risk of pulmonary embolism and DVT is increased in these patients. Thus, the occurrence of pulmonary embolism in this patient early in the study is not unusual event and most likely is due to uncontrolled hypercortisolemia. It is unclear whether this patient had intermittent worsening of hypercortisolemia at time of the event or the pulmonary embolism was due to the other factors. This patient was a responder in C-DM cohort and improved $AUC_{glucose}$ by 42% at Week 6 but worsened $AUC_{glucose}$ by 6% at Week 10 visit from Week 6 value.

13. Subject #23-001 (C-DM) a 41-year-old male with Cushing's disease developed one SAE, subcutaneous abscess in the right inguinal area that was considered unrelated to the study drug. The event occurred 4 months after initiation of the treatment with Korlym, patient was hospitalized and treated with antibiotics and surgical drainage; the study drug was continued during the event.

Medical Officer's comment:
Hypercortisolemia alters immune response, causes poor wound healing and increases risk of infection; thus an occurrence of skin infection in patients with Cushing's syndrome is not an unusual event.

<u>The narratives of the patients who developed SAEs in Study 415:</u>
1. Patient #10-002, a 41-year old male with ectopic Cushing's syndrome secondary to metastatic thymic carcinoid developed four SAEs: pneumonia, hypokalemia, hyperglycemia and interstitial lung diseases. <u>Hypokalemia was the only SAE that was considered a drug-related SAE</u>. Patient had medical history of diabetes, hypertension, asthma, metastatic lung carcinoma, hypokalemia, thymectomy and lobotomy. Patient was enrolled in Study 415 and initiated treatment with Korlym 1200 mg on July 22, 2010. The first SAE of pneumonia occurred (b) (6) after initiation of the treatment with Korlym; patient was hospitalized. The initial concern was that pneumonia was caused by Pneumocystis carinii, although no information about the microbiologic tests is provided. Patient was treated with antibiotics and prednisone, the study drug was continued. The event resolved. On (b) (6) patient developed the second SAE, severe hypokalemia (2.2-2.0 mEq/L); patient had been non-complaint with prior potassium supplements. The patient was admitted to the hospital and treated with intravenous and oral potassium supplementation. The patient had bigeminy on ECG and blood pressure was 180/92 mmHg. The potassium level normalized, metabolic alkalosis, heart rhythm and BP improved in 10 days. On December 28, 2010 patient developed a third SAE of hyperglycemia (blood glucose 326 mg/dL). The event resolved in 1 week with appropriate treatment. On (b) (6), patient developed the fourth SAE - interstitial lung disease. Patient was treated with everolimus at time of the event and was found to be febrile; chest x-ray demonstrated mild opacity in the left lobe and diffuse pulmonary vascular congestion. Patient was admitted to the hospital and treated with antibiotics, antiviral and anti-Pneumocystis medications. In spite of treatment, he developed

hypoxia, hypotension and was intubated. Korlym was interrupted. Everolimus was considered to be the cause of the pulmonary disorder and was discontinued on February 13, 2011. The pulmonary disorder resolved after everolimus discontinuation. Korlym was restarted at dose 900 mg daily on February 24, 2011.

Medical Officer's comments:
1. Hypokalemia is known adverse event associated with mifepristone treatment and is due to the activation of mineralocorticoid receptors by high levels of cortisol. Moreover, the uncontrolled hypertension that was reported in this patient during hypokalemia event was also most likely due to the activation of mineralocorticoid receptors.
2. The etiology of the first pneumonia event was not reported by the Sponsor; moreover X-Ray findings of bilateral infiltrates are suggestive of PCP. Without bacteriologic results Pneumocystis carinii pneumonia can not be ruled out completely. Occurrence of PCP is described in the literature in patients with Cushing's syndrome treated with antiglucocorticoid drugs including Korlym (Oosterhuis et al, 2007).
3. The second episode of pneumonia was considered due to everolimus, a kinase inhibitor that is indicated for the treatment of neuroendocrine tumors of pancreatic origin. One of the labeled AE associated with this drug use is a non-infectious pneumonia. Thus, the SAE is most likely due to everolimus, but without microbiologic testing for PCP the causality of the pneumonia event with Korlym use can not be ruled out completely.

2. Patient # 03-004, a 50-year old female with Cushing's disease developed SAE of melanoma in situ. Patient's dose of Korlym was 600 mg every other day.
3. Patient # 06-003, a 67-year old male with Cushing's disease developed two SAEs, arthritis and amyloidosis, and died during the study. The event of death is described in Section 7.3.1.
4. Patient # 07-004, a 49-year-old white woman with Cushing's disease developed dyspnea secondary to mild pulmonary edema and congestive heart failure, was admitted to the hospital and treated with furosemide. At the time of the event, the subject was taking 900 mg Korlym. The event resolved.
5. Patient# 09-001, a 63-year-old white female with Cushing's disease developed two SAEs: memory loss (resolved) and colorectal adenocarcinoma (underwent successful surgery). She was taking 1200 mg of Korlym at the time of the event.
6. Patient # 11-003, a 34-year-old male with Cushing's disease developed two SAEs: pulmonary embolism and esophageal carcinoma. Of note, the pulmonary embolism occurred during the treatment with Korlym in Study 400 *(refer to the subsection SAE in Study 400*), and continued into the Study 415; the event resolved completely. When patient was diagnosed with esophageal carcinoma, he was taking 1200 mg of Korlym at time of the second event.
7. Patient #16-002, a 46-year old male with Cushing's disease and history of anxiety had worsening of anxiety during Study 415. He was on Korlym 900 mg at time of the event.
8. Patient #22-001, a 52-year-old female with Cushing's disease developed pneumonia in 6 months after restarting treatment with Korlym 900 mg in Study 415. Patient was hospitalized and treated with antibiotics; the drug was discontinued. Patient also developed two events of hypotension. The first event of hypotension occurred on the day of the admission to the hospital and was associated with nausea; patient was treated with dexamethasone for 10 days in tapering

doses. The second event of hypotension occurred in 1 week after dexamethasone discontinuation (patient was still off the study drug); the treatment with dexamethasone was restarted and continued for 2 weeks. Eventually, pneumonia resolved and Korlym was restarted at dose of 300 mg once a day on May 12, 2011.
9. Patient # 23-001: 43-year old male with Cushing's disease developed subcutaneous abscess. The dose of Korlym was 600 mg at time of the event.

Non-Cushing's Corcept's studies
Total of 56 subjects who were treated with mifepristone in Corcept-sponsored studies in other indications developed SAEs (Table 41); the majority of the events were considered not related to the study drug. All SAEs events occurred in patients with ongoing medical conditions (e.g. depression or Alzheimer's disease); no SAEs occurred in the studies of mifperistone in healthy populations. The most frequent SAEs were worsening of depression, agitation, suicidal ideation and drug overdose. These types of events are not unusual in patients with major depression or Alzheimer's disease who are on multiple drug regimens, and thus, these SAEs are most likely related to the underlying condition and/or use of the concomitant medications and not to the study drug. Five SAE were listed as possibly or probably related to the study drug (depression, suicidal ideation, myalgia and fever, rash and grand mal seizure). Rash is known AE with the use of mifepristone and listed in Mifeprex label. No additional information was provided in the other four cases, thus, conclusion regarding a causal relationship between mifepristone and the events can not be drawn at this time.

Table 41. Listing of SAEs in Patients Who Received Mifepristone in Non-Cushing's Studies.

Study	Subject ID/ n of subjects	Event Preferred Term	Korlym Dose, mg
Studies in patients with major depression with psychotic features			
C1073-99-01	04-06	Suicidal ideation*	1200
	04-21	Suicidal ideation	50
	04-22	Suicidal ideation	50
	10-18	Suicidal ideation	600
C1073-02*^	5subjects	Aggravated depression	600 mg
	5subjects	Suicide attempt/ideation	600 mg
	1 subjects	Agitation	600 mg
	4 subjects	Worsening psychosis	600 mg
C1073-03	3 subjects	Suicide attempt	600 mg
	1 subjects	Worsening depression	600 mg
	049-162	Overdose	600mg
	015-290	High fever	600mg
C1073-04	03-218	Gravitational edema	600mg
C1073-06	1 subject	Suicidal ideation	300 mg
	2 subjects	Major depression	600 mg and 1200 mg
	17-0682	Asthma	1200mg
	28-0702	Homicidal and suicidal ideations	300mg
	29-0493	Anxiety	300mg
	29-0735	Rash and pleural effusion	1200 mg
	40-0425	Gastritis	600mg
	40-0789	Alcoholism	1200 mg
C1073-07	1 subject	Exacerbation of depression	600 mg
	11-108	Suicidal ideation	600 mg
	28-234	Elevated glucose and chest pain	600mg
C1073-09	20-187	Suicide attempt	600mg
	21-162	Concomitant drug toxicity	600mg
	24-176	Insomnia and depression	600mg
	24-261	Suicidal ideation	600mg
C1073-10	2 subjects	Pneumonia	600 mg
	06-07203	Orthostatic hypotension and subdural hematoma	600mg
	28-07286	Suicide attempt*	600mg
	28-07354	Depression	600mg
	30-7266	Dehydration	600mg
C1073-13	4 subjects	Major depression/ depression	600 mg
Study of Korlym in Prevention of Weight Gain			
C1073-200-1	1020	Myalgia/viral fever	600 mg
	1056	Enteric fever*	600 mg
C1073-205	211	Snake bite	
Study in patients with Alzheimer's disease (Study C1073-71)			
	01-042	Rash, nausea, decreased appetite, fever	300mg
	03-023	Anasarca	300mg
	04-026	Grand mal seizure*	300mg
	10-077	Repair of popliteal aneurysm	300mg

Source: Sponsor's table 17, Module 2, Vol 5, Summary of Clinical Safety, p.68- 72, modified.
* Subjects discontinued from the study because of the event; ^Four subjects discontinued from the study because of SAEs of depression and psychosis; SAEs that were considered drug-related by the Investigator are highlighted in yellow

7.3.3 Dropouts and/or Discontinuations

7.3.3.1 Overall profile of dropouts

Cushing's syndrome Studies (400 and 415)
Overall, 50 patients were enrolled in Study 400 and received at least one dose of Korlym; 34 subjects (68%) completed the study. Sixteen subjects were withdrawn from the study; of these, eight patients were withdrawn due to non-fatal AEs and two patients died. The Sponsor listed initially seven patients who were withdrawn due to AEs and one patient (# 08-003) who was withdrawn form the study because "she was too ill to travel" Later, in a summary of subjects with AEs leading to the study drug discontinuation, the Sponsor sated that this patient was withdrawn due to AE - progression of adrenal cancer. Thus, total of eight patients were withdrawn from the study due to non-fatal AEs.

Thirty of 34 patients who completed 6-month treatment in Study 400 entered the extension Study 415 and had data available for the analysis (cut-off date for the analysis May 27, 2011). Of those, 27 subjects were still continuing the treatment as of August 10, 2011. Three of 30 subjects discontinued treatment prematurely: one subject discontinued treatment because of AE, one subject died and one subject withdrew informed consent. Table 42 provides summary of patient dispositions, number of dropouts, and the reasons for drop-outs in studies 400 and 415.

Table 42. Patients Disposition and Reasons for the Withdrawal in studies 400 and 415

	Study 400, n (%)			**Study 415, n (%)**		
	C-DM	**C-HT**	**Total**	**Total**	C-DM*	C-HT*
Enrolled patients	29(58%)	21 (42%)	50 (100%)	30 (100%)	17	13
Total withdrawn	9	7	16 (32%)	3 (10%)	2	1
Reason for exclusion						
AE	3[1]	5[2]	8(16%	1 (3.3%)	1[5]	
Death	1[3]	1[4]	2 (4%)	1 (3.3%)	1[6]	
Consent withdrawn by subject	4	1	5 (10%)	1 (3.3%)		1
Non-compliance with study visits	1		1 (2%)			

[1]The last doses of Korlym were 300, 900, and 1200 mg, respectively; subjects were withdrawn in 39, 60 and 69 days after the treatment initiation, respectively.
[2]The last doses of Korlym was 300 mg in 3 subjects, 600 mg and 1200 mg in one subject each; subjects were withdrawn from the study in 60, 111, 114, 34, and 84 days after the treatment initiation, respectively.
[3] Subject #20-002 was on 300 mg of Korlym and died in 1 month after treatment initiation.
[4]Subject # 07-006 was one 1200 mg of Korlym and died in 112 days after treatment initiation.
[5]Subject was on 1200 mg for 3 months.
[6] Subject was on 300 mg for 17 days and died in 1 month after treatment initiation.
*Cohorts that the subjects were enrolled in Study 400.

7.3.3.2 Adverse events associated with drop-outs

Studies in Cushing's syndrome (400 and 415)
In Study 400, eight subjects (16.0%) were withdrawn from the study due to the ten TEAE (5 patients in C-HT, 3 patients – in C-DM cohorts). Of these 10 TEAEs, 3 events were not drug

related (progression of adrenal cancer in 2 subjects and worsening of cardiomyopathy in one subject) and 7 events were drug-related (fatigue, back and leg pain, worsening of fatigue, respiratory failure, gastrointestinal intolerance, fatigue, increase in pituitary tumor size). AE of fatigue led to the study withdrawal in three subjects, all other AEs occurred in one subject each. Three patients were withdrawn form the study due to SAE (respiratory failure, progression of cardiomyopathy and fatigue (considered as symptom of adrenal insufficiency by this reviewer, refer to Section 7.3.2). Two of three SAE (respiratory failure and adrenal insufficiency (fatigue) were considered as related to the study drug.

In the extension Study 415, only one subject was withdrawn from the study due to the AE-moderate endometrial disorder (possibly drug-related).

The narratives for the subjects who were withdrawn from the Study 400 due to the AEs:
1. Patient #01-003 (C-HT), 38 years old female, developed fatigue, back pain and leg pain. The events were rated as probably related to the study drug. This patient was treated with 300-900 mg of Korlym for 3 months; the last dose of Korlym was 300 mg. All events resolved without treatment.
2. Patient #07-007 (C-HT), 46 years old female, was withdrawn from the study because of the worsening of pre-existing fatigue. The event was considered as probably related to the study drug. The fatigue worsened in 1 month after initiation treatment with the study drug, but improved after drug interruption. The fatigue reoccurred after re-initiation of the treatment with 300 mg of Korlym and patients was withdrawn from the study permanently after she received total of 2- month of the investigational treatment.
3. Patient #07-009 (C-HT), 45 years old female with history of scleroderma developed respiratory failure that was considered possibly related to the study drug and was withdrawn from the study. She was treated with the study drug 300- 600 mg for approximately 1 month; the last dose of Korlym was 600 mg. The event resolved and was considered as SAE (refer to Section 7.3.2).
4. Patient #08-014 (C-HT), 30 years old male developed SAEs of nausea and asthenia considered as possibly related to the study drug and was withdrawn from the study due to the events (refer to Section 7.3.2). These symptoms were considered to be suspicious for the adrenal insufficiency by this reviewer. The event is discussed in details in Section 7.3.2. Briefly, patient developed first episode of severe nausea in 19 days after his dose was increased to 900 mg; the drug was interrupted for 1 month and patient was treated with dexamethasone. The attempt was made to re-initiate the treatment with lower dose of 300 mg, but patients developed nausea again, thus drug was discontinued permanently. The event resolved.
5. Patient #22-003 (C-HT), 52 years old male experienced an increase in the pituitary tumor size and was withdrawn from the study because of the event (refer to Section 7.3.5). The event was considered as possibly drug-related and was ongoing at the end of the study. Patient was treated with Korlym 300-1200 mg for 2 months; his last dose was 1200 mg.
6. Patient #07-003 (C-DM), 33 years old female, was withdrawn from the study because of the progression of adrenal carcinoma. Patient was treated with 300-1200 mg of Korlym for 2 months. The event was rated as not-related to the study drug.

7. Patient 07-008 (C-DM), 38 years old female was withdrawn from the study because of the progression of adrenal carcinoma. Patient was treated with 300-900 mg of Korlym for 40 days. The event was rated as not-related to the study drug.
8. Patient #08-003 (C-DM), 52 years old male had progression of pre-existing cardiomyopathy after he was treated with the 300 mg of the study drug for 5 weeks. The patient was withdrawn from the study because of the event, the event was considered as SAE that was not-related to the study drug (refer to Section 7.3.2). The event resolved.

The narratives for the subjects who were withdrawn from the Study 415 due to the AEs:
1. Patient # 24-004, a 45-year old female discontinued the study due to the development of multicystic endometrial complex (refer to Section 7.3.5). The event was reported as drug-related. Briefly, this patient was started on Korlym 1200 mg in Study 415 on December 15, 2010. At study entry the endometrial thickness was 4 mm, and increased to 11.0 mm after 3-month treatment with Korlym; patient was diagnosed with "multicystic endometrial echo complex" on March 17, 2011 and was withdrawn for the study.

Non-Cushing's Studies
The summary of the AEs that led to the study withdrawals in the other Corcept-sponsored studies is presented in Table 43.The most common AE that led to the study withdrawal in patients who received mifepristone were elevated LFTs and rash. Elevated LFTs were the most common AE that led to the study withdrawal in studies of mifepristone in prevention of weight gain: up to 29% of patients were withdrawn from those studies because of the abnormal LFTs. All subjects who were withdrawn from the studies due to the elevated LFTs received risperidone or olanzapine.

Table 43. Summary of AEs that Led to the Study Withdrawal in Non-Cushing's Syndrome Studies.

Study	Dosage regimen	Total enrolled, n (n of patients who received MIFE)	AE leading to the withdrawals	
			Total, n (n of patients who received MIFE)	AE by PT in subjects who received MIFE (dose)
PK studies in healthy volunteers, studies in special populations				
C1073-12	600 mg, two SD	50	1	Vomiting
C1073-27	1200 mg x 15 days	24	2	Rash*
C1073-19	1200 mg X 7 days	18	1	Nausea, dizziness [1]
C1073-23	MIFE: 1200 mg x 10 days DIG x 17 days	24	1	Viral syndrome
C1073-25	MIFE: 1200 mg x 10 days SIM: 40 mg , three SD	20	3	Rash[2]
Safety Studies in healthy volunteers				
C-1073-300	MIFE: 600 mg or 1800 mg x 14 days o PL or Pl + MOX	138 (105)	54 (43)	Rash[2]- 15 subjects (600 mg), 27 subjects (1800 mg), Pain in testicles -1 subject
C-1073-425 (HDL Study)	600 mg x 6 weeks	30	5	Rash- 4 subjects*, abdominal pain , fatigue, body ache -1 subject*
Studies in patients with MDD with psychotic features				
C1073-99-01	50 -1200 mg x 7 days	33	1	Suicidal ideation (1200 mg)
C1073-02	MIFE: 600 mg x 7 days or PL	208 (99)	11 (7)	Depression and psychosis
C1073-03	600 mg x 7 days	221 (105)	3 (2)	Psychosis , anxiety*
C1073-06	MIFE:300 mg -1200 mg x 7 days or PL	443 (332)	16(10)	Psychosis[3]
C1073-07	MIFE: 600 mg x 7 days or PL	258 (132)	4 (2)	Psychosis, elevated LFTs
C1073-09	MIFE: 600 mg x 7 days or PL	247 (124)	2 (1)	Death (suicide)
C1073-10	600 mg x 7 days in 28-day cycles	87	6	Pregnancy [4] and suicide attempt, hallucination, mania, depression, hematemesis and abnormal CBC
Studies in patients with Alzheimer's disease[9]				
C1073-71	MIFE: 300 mg x 16 weeks OR PL	81	8 (5[5])	Hypokalimia[2]-1 subject, rash[2], nausea and fever-1 subject*
Studies in prevention of weight gain[9]				
C1073-200	MIFE: 600 mg + OLA 5-10 mg x 3 weeks or PL + OLA	15	5 (4)	Rash-1 subject[2], elevated LFTs-3 subjects[6]
C1073-200-1	MIFE 600 mg + OLA 2.5-7.5 mg x 2 weeks or PL +OLA	59	26	Elevated LFT's-17 subjects[7], Rash-9 subjects[8]
C1073-205	MIFE 600 mg +RIS 0.5 -2 mg x 28 days or PL+ RIS	76	10	Rash-4 subjects, tremor-2 subjects, elevated LFTs-1 subject

MIFE-Mifepristone, PL-placebo, MOX-moxifloxacin, SIM-simvastatin, SD-single dose.
AE of rash are highlighted in yellow, elevated LFTs are highlighted in blue; *AE was considered as related to the study drug; [1] Subject with severe renal impairment; [2]The relation to the study drug was not specified; [3]The doses of mifepristone were not specified; [4]Pregnancy was diagnosed prior to the first dose administration of the study drug, thus subject was withdrawn from the study; [5]The AEs leading to the study withdrawal in three subjects are not specified; [6]All subjects received olanzapine; [7]Nine subjects received olanzapine, eight subjects received olanzapine + mifepristone; [8]Five subjects received mifepristone +placebo, four subjects received mifepristone +olanzapine.

The abnormal LFTs are listed AEs in the label for risperidone and olanzapine; thus most likely not related to mifepristone (refer to Section 7.3.5). The other common AE that led to the study withdrawals and was considered as related to mifepristone administration was rash. In Study 300, rash was the most frequent AE that led to the study withdrawal and developed in 49 subjects; 42/49 received mifepristone (the study is discussed in details in Section 7.3.5). The development of rash is not unexpected event with the use of mifepristone and is a listed AE in Mifeprex label. All other AEs leading to the withdrawal from the Corcept-sponsored studies were considered as not-related to the study drug or occurred in 1-2 subjects.

7.3.4 Significant Adverse Events

Adverse events leading to study discontinuation and serious adverse events have already been discussed in sections 7.3.2 and 7.3.3.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Adverse events based on mechanism of action of Korlym

The safety profile of Korlym can be anticipated to a large extent by its mechanism of action. Thus, such clinically significant adverse events as adrenal insufficiency, hypokalemia, endometrial thickening and vaginal bleeding, increased TSH levels and pituitary tumor growth may be associated with mifepristone. Overall, these adverse events are largely predictable and usually resolve with appropriate treatment or discontinuation of mifepristone.

Adrenal insufficiency (AI)
Mifepristone may induce adrenal insufficiency by blocking the biological effect of cortisol at tissue level. Because mifepristone does not decrease cortisol levels, the biochemical diagnosis of adrenal insufficiency is not possible. The diagnosis is based on the presence of clinical signs and symptoms of adrenal insufficiency, thus subjects need to be monitored closely for typical signs and symptoms of adrenal insufficiency such as fatigue, decreased appetite, nausea, hypotension, and hypoglycemia. Hyperkaliemia and hyponatriemia are not expected during the adrenal insufficiency induced by mifepristone because of the preserved mineralocorticoid effect. Thus, in all Corcept's studies subjects were monitored closely for the developing of signs and symptoms of adrenal insufficiency. All subjects with Cushing's syndrome in studies 400 and 415 were provided with a card identifying the potential risk for adrenal insufficiency; the dose of Korlym was carefully titrated throughout the studies. Overall, the overt adrenal insufficiency was uncommon in Cushing's syndrome studies (400 and 415). The Sponsor reported AI in two

patients; additionally 5 patients had two or more symptoms suspicious of AI. These five cases were reviewed, and, in this reviewer's opinion two more patients had possible AI (Table 44). Thus, a total of 4 patients with Cushing's syndrome developed AI during treatment with Korlym. Additionally, one patient who received mifepristone on compassionate use concomitantly with ketoconazole had an event of adrenal insufficiency for which she received corticosteroids; the event is discussed in details in Section 7.7.1. No additional information, including levels of cortisol at time of the event was provided. Ketoconazole can induce adrenal insufficiency as well by inhibiting cortisol synthesis, thus, the causality of the event with Korlym without additional information can not be established. No adrenal insufficiency was reported in other 27 supportive Corcept-sponsored studies.

Studies in Cushing's syndrome (400 and 415)

A total of two subjects with Cushing's syndrome (#22-001 and #24-001) developed three events of adrenal insufficiency reported as TEAEs in studies 400 and 415: two events in Study 400 and one event in Study 415 (Table 44). Two events of adrenal insufficiency were treated with dexamethasone; one event resolved with interruption of the study drug only. One episode of AI (patient # 22-0010) was reported as SAE and discussed in details in Section 7.3.2. Patient #24-001 developed total of two AI events: one-in Study 400 and one - in Study 415; both times patient was taking the same dose of Korlym 600 mg at time of the event.

Table 44. Summary of Subjects Who Experienced AI in Studies 400 and/or 415

Subject ID / age/ etiology of CS/ cohort	Case description	Dose of Korlym at time of the event	Treatment of AI
Study 400			
22-001* 50 y.o /F/CD C-HT	AI occurred after she was treated with Korlym for 5 months. The symptoms of AI were weakness, nausea, vomiting, decreased appetite, and hypokaliema. Of note, this patient had persistent nausea and dizziness for approximately 4 month prior to the development of AI. There was no hypotension or hypoglycemia reported. The event resolved. The subject resumed treatment with Korlym in Study 415 at a dose of 300 mg QD.	1200 mg	Dexamethasone X 7 days Korlym was interrupted
24-001 26-y. o/ F/ CD C-DM	AI occurred in 1 month after initiation treatment with Korlym. There was no hypotension or hypoglycemia associated with this event; no other information about symptoms is provided by the Sponsor. The event resolved and Korlym was restarted at dose 300 mg in 3 days.	600 mg	Korlym was interrupted
Study 415			
24-001 ** 26-y. o/ F/ CD	AI occurred in 2 months after the enrollment in the extension study and 1 month after the dose of Korlym was increased to 600 mg. Patient did not have hypotension or electrolyte abnormalities.	600 mg	Dexametahsone x 7 days

CD=Cushing's disease, F=female; * SAE

** Patient also developed groin abscess; most likely on-going infection triggered the AI.

Additionally, five patients in Study 400 developed two or more of symptoms suspicious of AI (dizziness, fatigue, weakness, hypoglycemia, hypotension, fatigue, lethargy, malaise, nausea, orthostatic hypotension, syncope, and vomiting) but not reported as AI. These subjects also received systemic glucocorticoids at the time of the event (Table 45). No patients in Study 415 had two or more symptoms suggestive of AI.

Table 45. Summary of Subjects with Suspected AI, but Not Reported as AI in Study 400

Subject ID/ cohort	Symptoms	Case description	Dose of Korlym at time of the event	Indication for the use of GC^	Relationship to the study drug
06-001 C-DM	Nausea, vomiting.	Was on Korlym 1200 mg for 79 days. In 4 days after the dose was decreased patient developed nausea and vomiting. DEX was administered x 10 days. The study drug was interrupted in 13 days after the onset of the events. The symptoms resolved and treatment with 600 mg Korlym was restarted.	900 mg	Possible drug effect	Possibly related
06-003* C-DM	Dizziness, syncope, orthostatic hypotension, fatigue	Patient had persistent fatigue since the study onset. In 2 month patient developed dizziness followed by syncope and orthostatic hypotension. The dose was interrupted and patient was given single dose of DEX 4 mg i.v. The dizziness and fatigue resolved, Korlym 600 mg was restarted; the hypotension persisted for 1 more month.	600 mg	Rule out AI	Possibly related
08-013 C-DM **	Nausea, vomiting	Was on Korlym for 1.5 month prior to the onset of severe nausea and vomiting. Dose was not interrupted, but patient received prednisone 60 mg for 8 days. Events resolved.	300 mg	Rhino-sinusitis	Vomiting-possibly related; Nausea-not-related
08-014 # C-HT	Fatigue, nausea, weakness, dizziness, hypotension	Patient had persistent severe fatigue and nausea since the study onset (for 2 months). Patient was treated with Korlym 900 mg for 1 month when he developed severe dizziness The study drug was interrupted, patient was administered DEX 8 mg i/v, dizziness resolved. DEX was continued for 9 days. Dizziness, weakness and hypotension reoccurred the next day after the last dose of DEX. Patient received HC 100 mg i.v and event resolved. Patient continued treatment with DEX x 10 days. Korlym was restarted at dose 300 mg; the fatigue and weakness persisted.	900 mg	Possible AI	Possibly related
24-005/C-DM	Fatigue, nausea, weakness	Was on Korlym 300 mg x 2 weeks. Nausea, fatigue and weakness developed in 5 days after the study drug was discontinued, patient was treated with DEX 0.5 mg four times a day x 2 days.	300 mg	Muscle weakness	Not related

GC=glucocorticoid; DEX=dexamethasone; HC=hydrocortisone; Patients who developed AI in this reviewer opinion are highlighted.
^Indication for the glucocorticoid administration as listed by the Sponsor (table 32, p. 121, module 5, vol 31)
* This patient had history of amyloidosis. Because amyloidosis can impact cardiac function, the Sponsor speculated that cardiovascular events may be due to fatigue and not to adrenal insufficiency.

** The nausea and vomiting in this patient was associated with acute exacerbation of sinusitis; patient received prednisone for the treatment of sinusitis. The investigator indicated that there was no adrenal insufficiency in this individual.
#Event was reported as SAE and led to study withdrawal, this event is described in details in sections 7.3.2 and 7.3.3.

Medical Officer's comments:
1. The Sponsor speculated that these five patients may have developed steroid withdrawal syndrome (SWS), a symptom complex similar to that of mild adrenal insufficiency (Bhattacharyya et al, 2005). Syndrome occurs usually after withdrawal of glucocorticoid therapy or, less frequently, after successful treatment of Cushing's syndrome and is due to the changes in circulating levels of cortisol. In this reviewer opinion, two patients (highlighted in Table 45) may have had AI (and not SWS): both patients had typical symptoms of AI such as nausea, vomiting (patient 06-001) and hypotension (08-014) that resolved with dexamethasone treatment. Acute onset of vomiting and hypotension are typical symptoms of adrenal insufficiency and not of steroid withdrawal syndrome.
2. In addition to those five patients with symptoms suspicious of AI, systemic glucocorticoids were administered during the Study 400 for the other than AI indications, including pneumonia, dyspnea due to the COPD, contrast agent reaction, stress of acute illness, prophylaxis of the secondary adrenal insufficiency, brain swelling, sinus infection, and pre-chemo treatment. All events were reviewed by this Medical Officer and were found not to be associated with adrenal insufficiency.

Endometrial thickening/bleeding
Mifepristone and other progesterone receptor modulator drugs induce well-known progesterone receptor modulator-associated endometrial changes (PAEC) including endometrium thickening with cystically dilated endometrial glands and combinations of features usually seen separately in normal proliferative and secretory endometrium. Vaginal bleeding occasionally may occur. Thickening of endometrium generally improves with the drug discontinuation.

Vaginal bleeding/endometrial thickening in Cushing's syndrome studies
In subjects with Cushing's syndrome, endometrial thickening was monitored by transvaginal ultrasound. Transvaginal ultrasound was performed in women with an intact uterus at the study entry and at Week 24 visit in the Study 400 and every 3 months in the Study 415. Endometrial abnormalities were defined as endometrial thickness > 5 mm and/or ovarian cysts > 2 cm in postmenopausal women and endometrial thickness > 20 mm and/or ovarian cyst > 5 cm in premenopausal women. Endometrial biopsy requirements were added to the safety evaluation at screening and Week 24 visits in Study 400 and at entry and Month 12 visit in Study 415. The endometrial biopsies were incorporated in the Study 400 after amendment 4 on November 19, 2009 and in Study 415 after Amendment 2 on April 27, 2010. Thus only, 7/35 females in Study 400 and 9/20 females in Study 415 had biopsy performed at screening and/or subsequent visits.

Study 400
Of 50 subjects enrolled in Safety population, there were 35 females (26 premenopausal females and 9 postmenopausal females). Twenty-nine females of 35 females enrolled in the study had

TVUS performed at baseline, and 26/35 females had TVUS performed at Week 24 visit. A total of 24/35 females had TVUS performed at baseline and Week 24 visit. In female subpopulation of patients with Cushing's syndrome mean endometrial thickness increased from baseline at Week 24 visit. The mean endometrial thickness at baseline was 6.14 mm ± 3.79 mm (median 5 mm, range 1-13 mm) and 2.75 mm ± 0.57 mm (median 3 mm, range 2-3.4 mm) in 23 premenopausal and 6 postmenopausal women, respectively. At Week 24 visit the mean values increased to 15.7 mm ± 14.3 mm (median 11 mm, range 4.8-55 mm) and 7.35 mm ± 5.10 mm (median 6.4 mm, range 1-17 mm) in 18 premenopausal and 8 postmenopausal women, respectively. There was a small decline in endometrial thickness at the 6-Week follow-up visit, but the endometrial thickness remained above mean baseline values (mean 14.1 mm and 5.5 mm in premenopausal (n=15) and postmenopausal women (n=6), respectively).

Increase in endometrial thickness was a common adverse event in women treated with Korlym and occurred in 10 of 35 females (30%) enrolled in the study; of these ten subjects, three experienced vaginal bleeding. Of note, 29/35 females had TVUS performed at baseline, and 24/35 females had TVUS performed at baseline and Week 24 visit. In most cases, the thickness decreased with treatment cessation; the thickness persisted at the 6-Week follow up visit in few premenopausal women only. Endometrial biopsies was performed in 6/10 females and showed benign endometrium consistent with PAEC changes in all but two cases where endometrial hyperplasia was detected (subject #11-001, simple non-atypical and subject # 24-006, complex atypical). One additional patient without endometrial thickness had biopsy performed as per protocol; the results were normal. Of note, none of the biopsies were performed at baseline, and all patients were treated with Korlym for some time prior to the first biopsy on the study. The Sponsor stated that subject #24-006 had endometrial changes prior to the onset of the study treatment (although no pathology report was provided). Subject # 11-001 underwent hysterectomy in Study 415; the final pathology report demonstrated benign inactive endometrium without polyp formation. Total of five premenopausal subjects (Subjects ## 06-001, 11-001, 22-002, 24-004 and 24-006) experienced vaginal bleeding in Study 400 (age 29-45 years). Three of five patients with vaginal bleeding were also diagnosed with endometrial thickness; all events of bleeding were considered related to the study drug. There were two additional mild TEAEs of single-day metrorrhagia without endometrial thickening (subjects #08-001 and #24-002); bleeding in subject #24-002 occurred 5 weeks after treatment discontinuation and was considered as not related to the study drug. No subjects discontinued the study due to the endometrial thickness or vaginal bleeding. No dose- and time-dependency for these TEAEs was established; the doses of Korlym varied from 300 mg to 1200 mg at the time of the event. Oral progesterone was used to treat endometrial thickening in all subjects during the time period between the last dose administration of Korlym in Study 400 and first dose administration of Korlym in Study 4l5; but was not always effective in inducing the withdrawal bleeding. Levonorgestrel releasing IUDs was used in one subject without effect on endometrial thickness. Vaginal bleeding resulted in gynecological procedures to treat the bleeding in four subjects; three of these subjects ultimately elected to have hysterectomies in order to continue Korlym treatment. Narratives for the patients who developed vaginal bleeding in studies 400 and 415 are presented in Table 46.

Medical Officer's comments:
One subject # 24-002 experienced mild spotting of one day duration 5 weeks after discontinuation of the study drug that was reported as not related to the study drug. The occurrence of vaginal bleeding in 5 weeks after discontinuation of the study drug is most likely unrelated to the Korlym treatment.

Study 415
The Sponsor listed 6/20 females who were diagnosed with AEs of endometrial hypertrophy in Study 415 (Sponsor's Table 6 "*TEAEs in 3 (10%) or more subjects by System Organ Class and Preferred Term (Safety Population)", Abbreviated Clinical Study Report: CI073-415, module 5, p. 28*). The review of the Listing 16.2.8.10 (*Listing of TVUS for Subjects with Intact Uterus, Study 415*) revealed four more subjects with endometrial thickness. Thus, total of 10 females had endometrial thickness that persisted from Study 400 or occurred in Study 415. A total of 9 females had endometrial biopsies performed; of these, four females had abnormal endometrial thickening. No endometrial hyperplasia was detected in all 9 cases. Three females with endometrial hypertrophy also experienced vaginal bleeding. Additionally, two patients experienced vaginal bleeding without endometrial thickness; one event was considered as not related to the study drug. Thus, total of five patients (age 31-50 years) experienced vaginal bleeding. One subject discontinued the study early due to the TEAE of abnormal endometrial findings (refer to the Section 7.3.3). No dose- and time-dependency for these TEAEs were established. Oral progesterone was used to treat endometrial thickness in 6 subjects – during the period between the last dose of Korlym in Study 400 and entry into Study 4l5, and in 2 subjects- during Study 4l5. The Sponsor stated that the combination of oral progesterone and withdrawal of the study drug resulted in reduced endometrial thickness. Levonorgestrel releasing IUDs were used in two subjects without effect on endometrial thickness.

Table 46. Summary of Subjects Who Experienced Vaginal Bleeding in Studies 400 and/or 415

Subject ID age/cohort	**Study 400**	**Study 415**
Patients with vaginal bleeding and endometrial thickness:		
06-001/ 34 y.o/ C-DM	Subject experienced multiple episodes of vaginal bleeding of 1-120 day duration. The first episode occurred in 3.5 months after the initiation of Korlym treatment (Korlym dose was decreased to 600 mg 2 days prior to this event because of nausea and vomiting). Patient remained on stable dose of Korlym 600 mg until the end of the Study 400, and experienced 4 more episodes of bleeding. Patient underwent TVUS at the end of the study after treatment discontinuation. TVUS showed endometrial thickness of 55 mm. The thickness decreased to 5 mm after dilation and curettage.	Patient was restarted on 600 mg of Korlym at study entry and developed endometrial thickening (32 mm) again in 3 months after treatment initiation. Multiple biopsies showed benign inactive endometrium with polyp formation. Vaginal bleeding reoccurred multiple times in spite of levonorgestrel-releasing intrauterine device insertion at the end of Study 400. Most episodes of bleeding resolved without treatment; patient underwent dilation and curettage once. Korlym was interrupted once because of vaginal bleeding. Eventually, thickness resolved, but the subject elected to have a hysterectomy; pathology showed benign

		inactive endometrium without polyp formation.
11-001/ 31 y.o/ C-DM	Subject experienced multiple episodes of vaginal bleeding of 1-34 day duration. The dose of Korlym was stable 1200 mg throughout the study. The first episode of bleeding occurred in 5 months after initiation of the treatment with Korlym; at the same time TVUS demonstrated endometrial thickness of 42 mm (increased from 3 mm at baseline). Endometrial thickening was 40 mm at 24-Week visit and 35 mm at 6-Week follow-up visit. Patient received medroxyprogesterone for 10 days after the last dose of Korlym. No biopsy was performed in Study 400, but endometrial biopsy performed between Study 400 and Study 415 showed simple non-atypical endometrial hyperplasia with polyp formation (proliferative with glandular crowding).	At study entry the endometrial thickening was considered to be resolved (16 mm); patient continued treatment with Korlym 1200 mg. Vaginal bleeding reoccurred in 6 month. TVUS demonstrated the endometrial thickness of 14 mm at that time; an endometrial biopsy showed inactive endometrium with cystic glandular dilatation and focal secretory changes. The dose of Korlym was interrupted because of the event; the drug was restarted at 600 mg. TVUS was repeated in 2 months and demonstrated endometrial thickening of 28 mm; the dose of Korlym was increased to 1200 mg. Serial TVUSs were repeated 1 month apart and demonstrated endometrial thickness of 27 mm and 15 mm, respectively. Eventually, thickness resolved, but the subject elected to have a hysterectomy; pathology showed benign inactive endometrium without polyp formation.
22-002/ 41y.o/ C-HT	Subject experienced multiple episodes of vaginal bleeding. The first episode of bleeding occurred at Week 20 visit. Patient was on stable dose of Korlym 1200 mg at that time; the drug was discontinued because of the event. Endometrial biopsy showed disordered benign endometrium with proliferative polyp formation. Endometrial thickness increased from 13 mm at baseline to 20 mm and to 25 mm at Week 24 Visit.	At study entry endometrial thickness resolved (12 mm) and vaginal bleeding stopped (patient received medroxyprogesterone acetate for 10 days between the studies). Korlym was started at dose 1200 mg. Vaginal bleeding reoccurred in 2 months in spite of the insertion of the levonorgesterel-releasing IUD. The subject elected to have a hysterectomy; pathology results showed disordered proliferative endometrium. The study drug was continued.
24-006/ 29 y.o/ C-DM	Subject experienced one episode of vaginal bleeding. She was treated with 1200 mg of Korlym. In 8 days after the last dose of the study drug, patient developed moderate vaginal bleeding. At screening, the endometrial thickness was normal, 12 mm, increased to 36 mm at Week 24 visit and was 35.8 mm at 6-Week follow-up visit. Patient underwent a D&C, pathology results showed complex atypical endometrial hyperplasia with polyp formation (glandular crowding and cellular atypia), squamous metaplasia with giant cell reaction and very minimal progesterone modulator-associated endometrial changes (PAEC). The pathologist commented that the absence of PAEC changes suggested that the endometrium was poorly	Did not participate in the Study 415.

	responsive to hormonal changes and these histological abnormalities may have been present prior to starting study drug.	
	Patients with vaginal bleeding **without endometrial thickness**	
15-005/ 42 y.o/ C-DM	Subject experienced one episode of mild vaginal bleeding in 4 days after the initiation of the treatment with Korlym. Bleeding continued for 9 days and resolved without treatment. Endometrial thickness was normal, 9 mm, at screening visit.	Did not participate in the Study 415.
08-001/ 44 y.o/ C-HT	Subject experienced a one-day of spotting on Day 1; endometrial thickness at baseline was normal, 1.1 mm.	Did not participate in the Study 415
24-002/ 37 y.o*/ C-HT	Subject experienced a one-day spotting in approximately 5 weeks after the completion of the treatment with Korlym. Baseline endometrial thickness was normal, 8 mm, and increased to 13 mm, but remained normal by Week 24.	Did not participate in the Study 415
10-003/ 50 y.o/ C-HT		Subject experienced episode of vaginal spotting of unknown duration. The endometrial thickness was normal (4.8 mm at study entry, 3.1 mm at Month 3 visit and 2.7 mm at Month 6 visit)
24-002/ 37 y.o*/ C-HT		Subject developed vaginal spotting on Day 88 of the Study 415. At study entry, the endometrial thickness was 13 mm, at Month 6 visit - 14 mm. An endometrial biopsy revealed "benign endometrium, disordered". Subject was previously diagnosed with endometrial thickness (20 mm) at 6-Week follow-up visit in the Study 400 and was treated with progesterone.

**Co nsidered as TEAE not related to the study drug*

Vaginal bleeding/endometrial thickness in the other supportive safety studies

In Study 425 evaluating the effect of mifepristone on HDL levels in postmenopausal females, there was an increase in endometrial thickness in several subjects in the mifepristone group at the Day 43 visit. The Sponsor did not specified how many subjects experienced this even, but stated that the thickness did not exceeded 5 mm which would be considered clinically significant in postmenopausal women. The endometrial thickness improved at Day 84. No vaginal bleeding occurred in the study. The Sponsor stated that no significant findings of vaginal bleeding or endometrial thickening were reported in other studies.

Hypokalemia

Korlym blocks glucocorticoid receptors and increases ACTH and cortisol levels. The elevated cortisol activates mineralocorticoid receptors and may induce hypokalemia, edema, hypertension and metabolic alkalosis. In overall Corcept's clinical program, hypokalemia occurred more

frequently and was more pronounced in subjects with Cushing's syndrome. This phenomenon may be explained by the fact that these patients are exposed to the hypercortisolemia for a longer period of time, they have high levels of baseline cortisol, and thus lower baseline potassium levels as compared to the patients without Cushing's syndrome. Therefore, subjects with Cushing's syndrome are at increased risk of developing hypokalemia with Korlym treatment. In both Cushing's syndrome studies (400 and 415), hypokalemia (potassium level ≤ 3.4 mEq/l) was a common AE.

Studies in Cushing's syndrome

Study 400

Hypokalemia was a frequent adverse event in the Study 400 and developed in 22/50 subjects (44%). One of 22 patients had hypokalemia at screening visit, and normal potassium values thereafter (Subject #07-003). Thus, 21/50 patients had drug-related hypokalemia during the study (Table 47). Seventeen of 22 subjects had hypokalemia that was reported as TEAEs. One subject had hypokalemia reported as SAE related to the study drug, this event is discussed in details in Section 7.3.2. Four subjects had severe hypokalemia (≤2.5 mEq/L). The events of severe hypokalemia occurred at Day 14, Week 12, 16 visits respectively; one subjects (#06-003) developed hypokalemia at 6-Week follow-up visit after he completed treatment with Korlym. All events of severe hypokalemia were preceded by declining of the potassium levels: 3 /4 subjects had previous low potassium values and one subject had previously normal potassium levels that were declining prior to the development of the event. Thus close monitoring of the potassium levels and early intervention might prevent the severe episodes. Six of 21 subjects had ≥ 1 event of hypokalemia during the study. Hypokalemia was frequently associated with signs of apparent mineralocorticoid excess such as edema and alkalosis, some of these patients also had worsened of hypertension during the hypokalemia event (number of subjects with concomitant hypertension is not summarized by the Sponsor). Eleven subjects were receiving diuretics at time of the event; the concomitant use of diuretics may have contributed to the development of hypokalemia. Most frequently hypokalemia was observed at Day 14, Day 28 and Week 6 visits (in 8, 10 and 7 subjects, respectively). Eight of 21 subjects had hypokalemia at screening or follow-up visits when they were not on study medications. The dose of Korlym varied form 300 to 1200 mg at time of the event. The conclusion regarding the dose- and time-dependency of the event can not be drawn at this time because of the frequent Korlym dose adjustments in individual subjects, use of concomitant diuretics and overall small study population. However, the increased frequency of hypokalemia during the first six weeks of the treatment with Korlym may be due to the more aggressive increase in Korlym dose at the beginning of the study; thus, this fact may warrant more frequent monitoring of the potassium levels during the first months of treatment. All events of hypokalemia resolved with appropriate treatment with oral and/or i.v potassium (doses 10 mEq-340 mEq daily) and /or spironolactone (doses 50 mg-300 mg daily) or eplerenone.

Table 47. Potassium Values and Korlym Doses in Subjects with Hypokalemia in Study 400

ID/ Cohort	Potassium, mEq/L (dose of Kolrym, mg^^)													
	Scr	D1	D7	D14	D28	W6	W8	W10	W12	W16	W20	W24	F/U	Treatment
01-001 C-DM	4.0	4.7	6.9	4.1	4.0	3.4 (300)	3.9	4.1	3.9	3.2 (300)	-	4.2	4.4	Potassium
06-003^ C-DM**	5.1	4.4	4.3	4.2	3.3 (600)	3.9	4.3	4.2	3.7	3.5	3.9	3.6	2.5-2.8	Potassium
007003^ C-DM	3.1	4.0	3.8	3.6	3.9	3.8								Potassium spironolact
07-006 C-HT**	3.3	3.8	3.5	4.0	3.4 (600)	2.9 (600)	2.8 (900)	3.5	3.4 (900)	3.5				Potassium spironolact
07-009^ C-HT**	4.1	4 3	4.4	4.0	3.3 (600)	-	-	-	-	-	-	4.1		Potassium
07-010 [a] C-HT	3.9	3.2 (300)	4.0	3.4 (300)	3.1 (600)	2.7 (600)	3.8	4.2	2.7 (1200)	2.1 (1200)	3.5	3.6	4.5	Potassium spironolact
08-014 C-HT**	-	4.4	3.8	3.1 (300)	3.8	4.2	3.1 (900)	3.7	4.2	-	-	-	4.5	Potassium spironolact
10-001^ C-DM	3.4	3.8	4.6	3.6	4.4	4.4	4.0	5.6	5.2	-	3.9	3 3- 3.5 (600)	2.6	Eplerenone spironolact
10-002 C-DM**	3.1	3.8	5.9	3.2 (300)	4.5	2.8 (0)	3.6	2.9 (900)	3.6	5.0	4.5	4.0	4.1	Potassium spironolact
10-003 C-HT	4.4	-	4.0	3.9	3.1 (600)	2.9 (600)	3.4 (900)	3.0 (900)	3.6	3.5	4.1	3.6	4.4	Potassium
10-004 C-DM**	4.4	3.4 - 3.6 (300)	4.5	4.7	4.6	4.2	4.3	4.4	4.5	4.2	4.5	4.3	4.3	Potassium
11-003 C-DM**	3.7	3 5	3.8	3.4 (300)	3.2 (600)	4.1	4.1	3.9	-	3.7	3.5	3.8	4.1	Potassium
11-004 C-HT**	3.7	3 9	3.8	3.4 (300)	3.7	3.7	4.2	4.2	3.7	3.8	3.8	4.0	3.7	Potassium spironolact
15-002 C-DM**	3.0	3.6	3.1 (300)	4.4	4.0	4.1	4.6	4.3	4.5	4.5	4.4	4.3	3.4	Potassium
15-005 C-DM**	4.9	4 3	3.8	2.5 (300)	3.1 (600)	-	-	-	-	-	-	4.8	-	Potassium spironolact
17-002^ C-DM	3.8	3.9	4.5	3.7	4.0	4.1	4.1	4.0	3.6	3.3 (1200)	4.9	4.2	4.6	
18-001 C-DM	4.1	4.0	4.9	3.3 (300)	3.1 (600)	4.3	3.9	3.8	2.2 (900)	4.4	2.9 (600)	5.1	4.1	Potassium spironolact
20-002 C-DM	4.7	4.4	3.4 (300)	4.0										Potassium

022001 C-HT	3.9	3.8	3.5	3.7	3.9	3.8	3.9	**3.1 (900)**	3.6	3.6	3.8	**3.2 (600)**	4.4	Potassium
22-003 C-HT**	4.9	4.4	3.8	3.7	**3.4 (600)**	**3.2 (600)**	**3.2 (900)**	**3.3 (900)**	-	-	-	**3.2 (1200)**	4.6	Potassium spironolact
24-001 C-DM	3.9	3.9	5.1	**3.4 (300)**	**3.4 (600)**	**3.2 (600)**	4.0	3.7	4.0	**2.9 (600)**	6.4	4.4	4.6	Potassium spironolact
24-006 C-DM	4.4	4.1	3.7	5.2	4.0	4.5	3.6	3.5	4.0	**3.3 (1200)**	6.7	**3.4 (1200)**	4.5	Potassium spironolact

Source: Sponsor's table 33, Module 5, Vol 31, CSR 400, p. 130-135, modified);
Low potassium levels are in red; events of severe hypokalemia are highlighted; D=day, W=week, spironolact=spironolactone.
^^ Dose of Korlym at time of the hypokalemia occurrence; ^Not reported as TEAEs; [a] Reported as a SAE; ** Subjects received concomitant diuretics during hypokalemia event (furosemide or thiazides).

Study 415

Overall, the largest decrease in potassium levels was observed at Month 6 visit. Total of 10 subjects developed 18 episodes of hypokalemia during the study; 6/10 subjects had abnormal potassium values that were not reported as AEs (Table 48). Four subjects were receiving diuretics at time of the hypokalemia event; the concomitant use of diuretics may have contributed to the development of hypokalemia. Four of 10 subjects had ≥ 1 event of hypokalemia during the study. Two of 10 patients had severe hypokalemia (< 2.5 mEq/L); one event of severe hypokalemia (2.2 mEq/L) was reported as SAE related to the study drug, this event is described in details in Section 7.3.2. Of note, the subject with SAE of hypokalemia was non-complaint with potassium supplements. No time dependency for the occurrence of hypokalemia was noticed: 3 subjects had hypokalemia at entry visit, 2 subjects had hypokalemia at Month 1 visit, 4 subjects had hypokalemia at Month 2 visit, 2 subjects had hypokalemia at Month 3 visit, 1 subject had hypokalemia at Month 4 visit, 2 subjects each had low potassium levels at Month 6 and 9 visits, 1 subject each had low potassium values at Month 12 and 18 visits. The doses of Korlym varied from 300 to 1200 mg at time of the event. All events of hypokalemia resolved with appropriate treatment with potassium and /or spironolactone or eplerenone; the doses of Korlym were not changed. Two subjects developed hypertension concomitantly with hypokalemia.

Table 48. Potassium Values and Korlym Doses in Subjects with Hypokalemia in Study 415

Subject ID	Potassium, mEq/L (dose of Korlym, mg^)										Treatment
	Entry	Mth 1	Mth 2	Mth 3	Mth 4	Mth 6	Mth 9	Mth 12	Mth 15	Mth 18	
06-001*	4.3	3.7	3.8	-	3.6	3.5	4.3	3.5	3.7	**3.3 (600)**	
06-003	**2.5** [a] **(300)**							4.5			Potassium, eplerenone
08-004*	4.0	3.9			3.8	**3.4 (1200)**	**3.1 (1200)**	3.7	3.5	4.3	Potassium, spironolact
10-001	**2.6 (600)**	**3.0 (900)**	**3.1 (900)**		3.5	3.9	**3.4 (1800)**	3.9			Potassium, spironolact
10-002 [b]	4.1	3.6	**3.1** [a,] **(1200)**	**2.2** [a, b] **(1200)**	**3.4** [a] **(1200)**	**3.1** [a] **(1200)**	3.7				Potassium
15-002*	**3.4 (300)***	4.5	4.7		4.5	4.8	3.8	4.1	4.7		
16-002*	4.7	**3.4** [a] **(900)**		**3.3** [a] **(900)**		3.6	3.5				Potassium, spironolact
18-001	4.1	4.2	4.0		4.1	3.9	4.2	**3.4** [a,c] **(600)**	4.3		Potassium, spironolact
21-001	5.0	3.5	**3.4 (1200)**	4.0		3.9	3.8	3.7			Potassium
24-001	4.6	3.8	**3.0** [a, c] **(600)**		4.1			4.3			Potassium, spironolact

Low potassium levels are in red font
^ Dose of Korlym at time of the hypokalemia occurrence is in parenthesis
[a] Reported as TEAEs
[b] This patient also developed a SAE of hypokalemia;
[c] Subjects had concomitant hypertension
*Subjects received concomitant diuretics during hypokalemia event (bumetanide, furosemide or thiazide diuretics).

Hypokalemia in non-Cushing's Corcept-sponsored Studies

No hypokalemia was observed in studies in healthy volunteers and in special populations (liver and renal-impaired). In studies in other indications hypokalemia most frequently occurred in Study C1073-71 (study in patients with Alzheimer's disease); the dosing with mifepristone was of the longest duration in this study (16 weeks). In this study, 10 /39 patients in mifepristone group had at least one potassium value below the lower limit of normal (< 3.6 mEq/L), the lowest potassium value observed was 2.8 mEq/l. One patient in the mifepristone group was withdrawn from the study because of hypokalemia (refer to Section 7.3.3). No subjects in placebo group had hypokalemia. In other studies of shorter duration in patients with psychotic depression and in prevention of antipsychotic medications-induced weight gain hypokalemia occurred only in few patients.

Increased TSH levels

Mild increase in TSH levels is not unexpected event with glucocorticoid antagonist treatment and may be due the alteration in pituitary-thyroid axes and central antiglucocorticoid effects of mifepristone (Heikinheimo et al, 1997; Johanssen et al, 2007). A direct effect of mifepristone within the thyroid gland leading to a compensatory increase in TSH levels is also suggested (Heikinheimo et al, 1997). In Corcept clinical program, the TFTs changes were observed most frequently in studies with the longest treatment duration: in studies in Cushing's syndrome (6 months) and in Alzheimer's disease (6 weeks). Thus, TFTs changes might be associated with longer exposure to the study drug. In general, the event was predictable by routine monitoring of TFTs levels and resolved with appropriate levothyroxine treatment or discontinuation of Korlym in the majority of the patients.

Studies in Cushing's syndrome

Study 400

There was an increase in mean TSH levels from 1.2 ± 1.3 mU/L at baseline to 4.2 ± 5.6 mU/L at Week 24 visit; levels returned to the baseline values at 6-Week follow up visit (1.2 ±1 mU/L). The mean FT4 levels decreased by the end of the study from baseline and returned to the baseline values at 6-Week follow up visit (14.4 ±3.4 pmol/L, 12.4 ± 3.1 pmol/L and 13.7 ± 3.4 pmol/L, respectively).

Eight subjects with normal TSH values at baseline had high TSH values at the end of the study; three subjects had final TSH levels > 10 mU/L, including one subject with a TSH level of 32.8 mU/L (Table 49). TSH levels returned to normal levels in all 8 subjects. Of these eight subjects, seven had decline in free T4 levels. FT4 levels returned to normal at 6-Week follow up visit in 4/7 subjects; one subject had further decrease in FT4 levels at 6-Week follow-up visit. One of eight subjects with elevated TSH levels at the end of the study was diagnosed with hypothyroidism at the study entry and was started on levothyroxine replacement therapy; the additional subject was started on levothyroxine therapy at Week 24 visit. TSH levels also increased in one of 8 subjects who had low or undetectable TSH levels at baseline. The elevated TSH values in this subject resolved with levothyroxine dose reduction (subject # 15-002). TSH levels remained very low in the other seven subjects. Six of those subjects had

Cushing's disease and may have had central hypothyroidism due to the previous surgery and/or radiation.

Table 49. Summary of Subjects with an Elevation in TSH in Study 400

Subject ID	Screening visit		Week 24 visit			6-Week follow up visit		Treatment with levothyroxine
	TSH* mu/L	FT4** pmol/L	TSH mU/L	FT4 pmol/L	Last Korlym dose	TSH mu/L	FT4 pmol/L	
10-002**	12.9	16.7	32.8	7.7	1200	2.0	11.6	
11-003	1.69	12.9	6.47	9.0	1200	3.54	11.6	
16-002	1.14	15.4	6.72	11.6	900	1.29	9.0	
17-002	1.4	15.4	9.52	12.9	1200	2.93	12.9	
21-001	1.13	12.9	6.53	12.9	1200	1.57	15.4	
22-001	1.37	12.9	13.5	12.9	600	1.0	14.2	75 µg daily started after the study completion
22-002	5.36	16.7	6.3	15.4	0^	1.73	14.2	100 µg daily started at screening
24-002	1.61	12.9	13.85	9.0	1200	2.01	10.3	

Source: Sponsor's table 36, Module 5, Vol 31, CSR 400, p. 139, modified.
*TSH normal range: 0.4 - 5.5 mU/l; **Free T4 normal range: 10.3 - 23.2 pmol/l; ^ The treatment was terminated at Week 20 visit, but the TSH was drawn at Week 24 visit.; The abnormal TSH and FT4 levels are in red font
** TSH and freeT4 were normal in Study 415.

Study 415

In 20 subjects who entered the study and received treatment with Korlym for at least 12 months mean TSH levels increased to 2.6 ± 2.7 mU/L from 1.15 ± 0.9 mU/L (n=30) at baseline. The mean FT4 levels remained unchanged (13.7 ± 3.4 mU/L and 13.28 ± 3.8 mU/L at baseline and in 12 months, respectively). Four subjects had abnormal TSH values (5.76-12.9 mU/L) during the study, but normal FT4 levels (Table 50). One additional subject #06-002 had AE reported as hypothyroidism, but TFTs were normal.

Table 50. Summary of Subjects with an Elevation in TSH in Study 415

Subject ID	Baseline		Abnormal values				Treatment
	TSH mU/L	FT4** pmol/L	TSH mU/L	FT4 pmol/L	Visit	Dose of Korlym at time of the event, mg	
07-004	2.39	16.7	8.99	11.6	Month 18	900	LT4 dose was decreased prior to Month 6 visit^
16-002*	1.29	9	6.02	14.2	Month 6	900	
21-001	1.57	15.4	5.76	11.6	Month 6	1200	
22-002	1.73	14.2	12.9	11.38	Month 6	1200	On stable LT4 dose

* AE reported as hypothyroidism ; **Normal range is 10.3-23.2 pmol/l; ^ Patient had TSH 4.35 mU/L and FT4 11.6 pmol/L at Month 6 visit. Subjects who had abnormal TFTs in Study 400 are highlighted.

Other non-Cushing's Corcept's studies
No clinically meaningful changes in TFTs were found in the majority of the studies in healthy volunteers, in patients with psychotic depression (C1073-99-0l, C1073-04 and C1073-06) and in prevention of weight gain. T4 levels decreased below normal levels in three patients who were treated with mifepristone in Alzheimer's study (C1073-71); the levels returned to normal values at the post-study follow-up visit.

Increase in pituitary tumor size in patients with Cushing's disease in studies 400 and 415
Glucocorticoid receptor blockade may lead to increase in ACTH production due to the loss of a negative feedback loop and may induce tumor volume expansion. This phenomenon of tumor volume expansion is a well-known rare adverse event that has been described in patients with Cushing's disease after adrenalectomy. Thus, to explore the effect of Korlym on tumor volume, MRI was performed in patients with Cushing's disease at the beginning and end of the Study 400. The initial MRI readings performed at the local sites were submitted in the original NDA. Thus, the Sponsor reanalyzed MRI at a central reading facility and submitted the results of this analysis in 4-month update (refer to Section 7.7.1). Forty three patients with Cushing's disease were enrolled in the studies; 41/47 patients underwent MRI of pituitary and 37 patients had at least one post-baseline MRI. The median time of treatment was 5.7 months (range: 0.9-27.1 months). Four subjects in Study 400 and two subjects in Study 415 had possible increase in tumor volume. Overall, the increase in tumor size was small or inconclusive in most cases and occurred in few patients only. The event did not raise any significant safety concerns with Korlym use at present time, but longer treatment duration may be required to detect clinically significant changes.

Study 400
Two subjects (# 07-010 and # 22-003) had increase in pituitary tumor size in Study 400; both events were considered as related to the study drug. Subject # 22-003 was withdrawn from the study because of the tumor enlargement and discussed in Section 7.3.3. During retrospective analysis submitted by the Sponsor in 4-month update two additional subjects (#03-004 and #10-003) were found to have progression in tumor size that was not reported in the original NDA. Briefly:

- Subject #22-003 had previous pituitary surgery and pituitary radiation with significant residual pituitary tumor. MRI at Week 10 visit (dose of Korlym was 1200 mg) demonstrated mild enlargement of the mass (32 mm x 52 mm) from baseline (27 x 46 mm), thus the subject was discontinued from the treatment. MRI at the 6-Week follow-up visit showed no further changes in tumor volume. Of note, the tumor was unstable prior to the study entry: the tumor growth was evident when MRI images performed 4 months prior to the study entry and at the screening visit were compared. This patient was eventually diagnosed with pituitary cancer with liver metastasis.
- Subject # 07-010 was diagnosed with possible microadenoma (3 mm) at Week 10 and Week 24 visits; the pituitary adenoma was not reported on the screening MRI. In this Medical Officer's opinion, this tumor may represent pituitary incidentaloma that occurres in up to 10% of subjects in general population, or the tumor was present at baseline but was not detected by MRI because of the small size. Of note, this tumor was not confirmed

during the retrospective analysis of MRI submitted in 4-month update (refer to Section 7.7.1).

- Subject # 03-004 had a tumor progression in one dimension only at Week 24 (from 9.5 mm to 11.8 mm).
- Subject # 10-003 was found to have initial regression of the pituitary tumor at Week 10 (7.5 mm x 6.5 mm) from baseline (8.3 mm x 8.8 mm) followed by the progression at Week 24 (9 mm x 9 mm). In this reviewer opinion, the difference in the size of tumor at the last visit as compared to the baseline visit was small and might be due to the reading error (change 0.7 mm x 0.2 mm).

Study 415

Two subjects (#08-004 and 08-005) had slight increases in pituitary tumor size at Month 6 visit; the tumors remained stable on the subsequent MRI. Both subjects were asymptomatic. Retrospective analysis of pituitary MRI (refer to Section 7.7.1) confirmed that an invasive adenoma in subject # 08-004 increased in size from 13 x 15 mm at baseline in Study 400 to 15.5 x 18.6 mm at Month 25 visit in Study 415. The increase in tumor size in patient #08-005 was not confirmed by this analysis. The doses of Korlym were 1200 mg and 600 mg in these subjects, respectively. ACTH levels slightly increased at Month 6 visit from baseline visit in both subjects (from 39 ng/mL to 121 ng/mL and from 50 ng/ml to 72 ng/mL, respectively) and remained stable thereafter.

7.3.5.2 Ophthalmologic effects

Retinal atrophy was observed in albino rats after one year of treatment with mifepristone (refer to Section 4.3 and to Dr. Patricia Brundage's review). Thus, ophthalmological evaluation was incorporated in studies 415 and 425 following a request from the FDA on February 18, 2010, to perform ophthalmologic monitoring in all studies that are longer than 6 weeks. No abnormal findings were reported in the evaluated patients. Of note, all patients in Study 415 had been on Korlym already for over 6 months, thus no baseline readings were available. The subjects in Study 425 had short exposure to mifepristone (6 weeks) only. Thus, no conclusion about ophthalmologic changes associated with Korlym treatment can be drawn at this time; longer treatment duration may be required to detect clinically significant changes.

Study 415

The extensive ophthalmological evaluation including slit-lamp and retinal exam was initiated after amendment 3 to the protocol in November 2010. The subjects had to have the complete eye exams at entry into the extension study or as soon as possible for those subjects who entered the study prior to amendment 3 and every 6 months thereafter. All subjects had been treated with Korlym already for over 6 months in studies 400 and 415, thus no baseline readings were available. Twenty of 30 subjects enrolled in the study had ophthalmological examination. All evaluated patients had at least 12 months of cumulative exposure to the study drug in both studies (400 and 415); 5/ 20 patients had at least 24 months of exposure and 12/20 patients had at least 18 months of exposure. There were no abnormal ocular findings

considered to be Korlym-related. Two subjects with DM had diabetic retinopathy and two subjects had hypertensive retinopathy.

Study 425
Complete eye examinations were also performed during the Study 425 evaluating effect of mifepristone on HDL level in postmenopausal females. The eye exam was performed at screening, after the final treatment on Day 43 and on Day 84. There were no significant safety findings related to mifepristone reported in this study. Of note, patients in this study had much shorter exposure to mifepristone (6 weeks) compared to exposure in Cushing's studies.

7.3.5.3 QT interval prolongation

Small, but statistically significant, dose-related QT and QTc-intervals prolongation was found in the chronic toxicity dog study (refer to Section 4.3 and to Dr. Patricia Brundage's review). Thus, the Sponsor further investigated the QT effect of Korlym in healthy subjects in Study 300. The study design and its results are discussed in details in Section 7.4.5. The results of the study were reviewed by Interdisciplinary Review Team for QT Studies (refer to the full review in DARRTS). As per Review Team, the study was inconclusive, because the assay sensitivity was not established and, as the largest lower bound of the two-sided 90% CI for the placebo adjusted, baseline-corrected QTcI ($\Delta\Delta$QTcI) for moxifloxacin was less than 5 msec. Therefore, small increase in QTc interval cannot be excluded.

The QT interval prolongation was also monitored by ECG in Corcept's studies in Cushing's syndrome and in some other supportive studies.

Studies in Cushing's syndrome
Study 400

Subjects underwent l2-lead ECG at the screening visit, on Day 14, and at the follow-up visit. ECG results were machine-read and abnormalities interpreted by the Investigators. The QTc intervals in Table 51 were reported as QTcB and were read by machine or calculated. QTcF values were calculated from the QTcB data and heart rate data measured at the same time. Overall, no clinically significant changes in heart rate, QTcF interval or PR interval were found. The mean heart rate was 77 ± 16.4 bpm at baseline and remained unchanged at Day 14 (77 ±15.1 bpm). The PR interval was slightly longer on Day 14 (151 ± 24.3 msec) compared to the screening value (148 ± 23.5 msec); the change from baseline of 2.8 msec were most likely not statistically significant (90% CI: -0.3 to 5.9 msec). QRS and QTc interval were unchanged throughout the study. No significant changes in mean QTcF values were observed during the first 14 days of the treatment with Korlym: QTcF was 414 ± 23.3 msec at baseline and 413 ± 24.0 msec at Day 14 visit; QTcF change from baseline to Day 14 was –0.7 msec and were not statistically significant (90% CI: -5.1 to 3.7 msec).

Table 51. ECG Intervals (Change from Screening to Day 14 Summary Statistics)

ECG Parameter (n=48)	Mean (SD)	Median	Min, Max	90% CI
Heart Rate (bpm)				
Screening	77.10 (16.383)	74.50	53.0, 122.0	73.14, 81.07
Day 14	76.98 (15.069)	74.50	44.0, 114.0	73.33, 80.63
Change from Screening to Day14	-0.13 (11.066)	0.00	-26.0, 23.0	-2.81, 2.56
PR Interval (msec)				
Screening	148.44 (23.468)	144.00	102.0, 200.0	142.75, 154.12
Day 14	151.23 (24.308)	145.00	102.0, 204.0	145.34, 157.12
Change from Screening to Day14	2.79 (12.838)	2.00	-30.0, 40.0	-0.32, 5.90
QRS Interval (msec)				
Screening	88.92 (15.022)	86.00	66.0, 154.0	85.28, 92.55
Day 14	87.77 (18.451)	87.00	37.0, 164.0	83.30, 92.24
Change from Screening to Day14	-1.15 (9.394)	0.00	-43.0, 16.0	-3.42, 1.13
QTcF Interval (msec)				
Screening	413.62 (23.285)	413.19	375.5, 475.7	407.98, 419.26
Day 14	412.92 (23.961)	409.70	371.3, 501.3	407.12, 418.73
Change from Screening to Day14	-0.70 (18.155)	-2.07	-37.9, 51.7	-5.10, 3.70

Source: Sponsor's table 37, Module 5, Vol 31, CSR 400, p 142, modified;
Changes in PR intervals are highlighted.

Overall, there were five subjects with either QTcF exceeding 450 msec or with QTcF changes of more than 30 msec at Day 14 from baseline (Table 52). Four of these subjects were females (gender-adjusted upper limit of a normal QTcF interval for females is 470 msec). Three of four females had QTcF ≥ 450 but < 470 msec at baseline. One female #08-003 had QTcF interval at baseline of 475.7 msec and also had a bundle branch block with QRS width of 154 to 164 msec. Subject #06-003 was the only male in this group and had a QTcF < 450 msec at screening with an increase of 8 msec from baseline (QTcF interval was 454 msec on Day 14). Subject #11-004 had a normal QRS interval and QTcF change at Day 14 visit of 52 msec from baseline; the QTcF increased from 396 msec at baseline to 448 msec on Day 14. The value returned to normal (417 msec) at the follow-up visit.

Table 52. Summary of Subjects with QTcF ≥ 450 msec or an Increase in QTcF ≥ 30 msec (original NDA data)

Subject ID	Cohort	Sex	Age (yrs)	Korlym		Baseline ECG values		Day 14 ECG values		Change in QTcF (msec)
				Dose at Day 14 (mg)	Trough level at Day 14 (ng/mL)	QTcF (msec)	Heart Rate (bpm)	QTcF (msec)	Heart Rate (bpm)	
01-001	C-DM	F	64	600	1100	466.1	85	445.8	90	-20.3
06-003	C-DM	M	67	300	952	446.1	80	454	72	7.9
07-009	C-HT	F	45	300	2490	450.3	70	451.9	75	1.6
08-003	C-DM	F	60	300	1690	475.7	78	501.3	98	25.6
11-004	C-HT	F	48	300	1450	395.8	73	447.5	62	51.7

Source: Sponsor's table 38, Module 5, Vol 31, CSR 400, p. 144
Red font indicates a value ≥ 450 msec or an increase ≥ 30 msec.

The ECG data from these five subjects was re-evaluated by a cardiologist and the results were submitted in 4-month safety update (refer to Section 7.7.1). Four of five originally identified subjects with QTcF prolongation or Δ QTcF > 30 msec still had abnormal values; one patient (# 07- 009) did not have any outliers values after correction. Subject # 11-004 had longer than originally machine-read QTcF value (406 msec vs. 396 msec). This patient was originally reported as having abnormal Δ QTcF of 51.7 msec; the Δ QTcF remained abnormal after correction (+39 msec). Patient # 01-001 also had left bundle branch block with prolonged QRS at baseline (126 msec) and on Day 14 (128 msec). The Sponsor stated that an overcorrection of QTcB at heart rates above 60 bpm contributed to the prolonged reported value in both cases and corresponded to a QTcF of 419 msec and 472 msec, respectively. Additionally, eleven subjects exhibited outlier values for QTcB interval (Table 53). The Sponsor considered the Bazett correction algorithm an inappropriate, as it overcorrects the QT value at elevated heart rates (Malik, 2010).

Table 53. Listing of Subjects with QTcB ≥ 450 msec or a Change in QTcB ≥ 30 msec

Subject ID	QTcB Value (msec)			Korlym on Day 14	
	Screening	Day 14	6-Week follow-up	Dose (mg)	Trough level (ng/mL)
01-003	436	456	421	600	3080
06-003	468	468	529	600	952
08-003	497	544	532	300	1690
08-014	416	427	471	600	1270
10-002	442	438	490	300	3050
11-002	394	414	430	300	1080
11-004	409	450	418	300	1450
17-002	442	440	452	300	991
20-002	439	452	ND*	300	3540
21-001	388	410	424	300	1450
22-001	428	454	419	300	2920

Source: Sponsor's table 39, p. 145, vol 31; Red font indicates value ≥ 450 msec or a QTcB change of ≥ 30 msec.
*Subject 20-002 died during the study and did not have any 6-Week follow-up visit values.

Study 415

In Study 415, a 12-lead ECG was obtained at entry and every 3 months thereafter (after addendum 4 to the protocol on February 2011). Two subjects had clinically significant ECG findings on Day 1; both subjects were administered 1200 mg of Korlym. Subject #08-004 had first degree atrioventricular block; subject #10-002 had mildly prolonged QT interval. Both events were reported as unrelated to the study drug.

Medical Officer's comment:
The drug has propensity to prolong QT interval as was demonstrated in Study C-1073-300, thus, the relationship of QT prolongation in these two subjects with the study drug can not be excluded completely.

Non-Cushing's Corcept's studies
Overall, no clinically significant ECG changes with the use of mifepristone were reported in any of the trials; however the small number of patients and short duration of the studies precludes any meaningful assessment of the findings.

Special safety studies, studies in special populations and PK studies in healthy volunteers
No clinically significant ECG abnormalities were reported in the rechallenge Study 301 in Study 425 and in studies in special populations. The results of TQT Study (300) are discussed in details in Section 7.4.5.

Abnormal ECG findings in PK drug-drug interaction studies were reported in Study C1073-16 only (evaluation of the effect of single and multiple doses of 1200 mg of Korlym and 40 mg fluvastatin). Mean ECG parameters remained within normal limits from screening to final visit. Two subjects had prolongation of the postdose corrected QT intervals: one subject had an increase from 418 msec at baseline to 464 msec and the other one had an increase from 405 msec at baseline to 459 msec. These QTc prolongations were not reported as TEAEs.

Studies in other indications
There were no significant ECG findings in studies for the prevention of weight gain.

No significant effect of mifepristone on mean QTc intervals in Alzheimer's disease population was demonstrated. A total of nine patients (six patients in mifepristone group) had QTcF values exceeding 450 msec or a change from baseline (ΔQTcF) exceeding 30 msec. No correlation of mifepristone plasma concentrations with QT changes was demonstrated. The data was reanalyzed by cardiologists and results were submitted in 4-month safety update (refer to Section 7.7.1). Four patients initially reported as having prolonged QTcF interval or Δ QTcF were considered to have no ECG abnormalities after correction. Four of five patients with still abnormal values had either a longer (3 patients) or the same (1 patient) QTcF interval at screening as originally identified by machine. One patient on placebo had a longer but still normal ΔQTcF of 29 msec (from 434 msec a baseline to 463 msec at the Day 14 visit). None of the patients exhibited a ΔQTcF > 30 msec.

The majority of subjects with major depression with psychotic features who received mifepristone had normal ECG or had not clinically significant ECG changes; the only ECG changes were observed in studies C1073-02 and C1073-10:

- Study C1073-02

No changes in the QTc interval were recorded. However, the Sponsor stated that there were eight subjects in each treatment group (drug and placebo) who had ECG reading that worsened from screening to Day 7, but did not specified what these changes were.

- Study C1073-10

Overall, the mean ECG changes from baseline were not considered to be clinically relevant. The shifts in QTc results during the first retreatment cycle were: 18 patients (46.2%) had normal QTc intervals at both Day 1 and 7 assessments; 12 patients (30.8%) had abnormal values at both Day 1 and 7 assessments; two patients (5.1 %) improved in QTc intervals at Day

7; and seven patients (17.9%) had worsen in QTc intervals at Day 7. No QTc values were greater than 450 msec. The shifts in QTc results following the other retreatment cycles were generally consistent with the results during the first retreatment cycle.

7.3.5.4 Decreased HDL levels in patients with Cushing's syndrome

Decrease in HDL levels was noticed in patient with Cushing's syndrome during the Study 400. The largest mean reduction in the HDL levels occurred at Week 6 visit (the levels decreased by 0.576 ± 0.9165 mmol/L and 0.470 ±0.5381 mmol/L, respectively). At 6-Week follow-up visit, HDLl levels returned to their baseline levels (refer to Section 7.4.2). Thus, the Sponsor further analyzed the effect of mifepristone on HDL levels in special safety Study 425. Overall conclusion of this study was that mifepristone m decreases HDL particle concentrations but preserves reverse cholesterol transport. This study is discussed in details in Section 7.4.5. The HDL-changes observed in Study 415 were consistent with the trend in HDL values observed in Study 400. Mean and median HDL values decreased from baseline again after the initiation mifepristone treatment; mean reduction was 0.37 mmol/L, 0.22 mmol/L and 0.37 mmol/L by Month 6, 12 and 18, respectively (refer to Section 7.4.2). The Sponsor concluded that the clinical importance of the decline in HDL levels in patients with Cushing's syndrome is unclear, since there were improvements in the other important cardiometabolic measures, such as glucose and weight.

7.3.5.5 Adverse events that occurred with increased frequency in Corcept clinical program of Korlym

Such adverse events as rash, fatigue, nausea and headache were observed with increased frequency in overall Corcept's clinical program during mifepristone administration. All these events are listed adverse events in Mifeprex label. Additionally, abnormal liver enzymes levels were also observed with increased frequency in studies of mifperistone in prevention of antipsychotic medications-induced weight gain; thus, these findings will be also discussed here.

Rash

The association of rash with mifepristone is well documented event in literature and also listed AE in Mifeprex label. Rash associated with exposure to mifepristone is a general macular-papular eruption that involves the trunk and can extend to the extremities and face. Pruritus is common but systemic symptoms are rare. Rash associated with mifepristone was frequently observed across Corcept's sponsored studies. . In overall Corcept's clinical program, individuals with Cushing's syndrome have a much lower incidence of mifepristone-related rash than seen in healthy subjects. The highest incidence of rash associated with mifepristone use was observed in Study 300 (ECG trough Study) in healthy volunteers. The rash does not recur on re-exposure to the drug as indicated in the re-challenge Study 301 (refer to Section 7.4.5). All events of rash were treated with topical agents, antihistamines and/or glucocorticoids and resolved over time or after discontinuation of mifepristone. No evidence of Steven-Johnson syndrome or Toxic Epidermal Necrolysis has been reported in any of the trials

Rash in Cushing's syndrome studies

The appearance of rash was monitored throughout both Studies (400 and 415); the study protocols required careful documentation of any clinically significant Korlym-induced rash.

Study 400

Ten subjects experienced a TEAE of mild to moderate papular or erythematosus rash; three events were considered as related to the study drug (subjects # 01-003, 03-004, and 16-002). The drug-related AEs of rash were reported as red spots on face and neck, worsening of lupus rash and drug rash; the doses of Korlym were 600 mg, 600 mg and 300 mg at time of the events. The other not-related to the study drug AEs of rash were described as eczema-like condition on the hand, erythematosus rash, pustules on scalp, rash due to the shrimp allergy, rash on the lower neck and hand, recurrent rash in groin, and worsening skin yeast infection. Subject with lupus rash had the dose of Korlym reduced. Four other subjects with not-related to the study drug rashes were treated with medication. By the end of the study, the majority of the rash events had resolved (7/ 10 subjects); the rash in three subjects was ongoing (eczema like condition on hands, skin yeast infection and erythematosus rash) at the end of the study. Overall, the number of subjects who developed rash was small, the doses of Korlym varied in all subjects, no detailed information about the duration of the event in the individual subjects were reported, thus, the conclusion regarding the association of all 10 events with the study drug or dose of the study drug can not be drawn at this time.

Study 415

Three subjects developed rash in the study. The rash was considered drug-related in two subjects: one subject was on 300 mg of Korlym (had worsening of lupus rash; the dose was interrupted) and one subject was on 1200 mg of Korlym daily. Of note, patient with history of lupus also had episode of rash in Study 400. The third patient had a rash due to the poison ivy; the event was considered as unrelated to the drug.

Rash in non-Cushing's Corcept's studies

Special Safety Studies

Studies 300 (TQT Study in healthy volunteers) and 301 (rechallenge study).

Rash in the Study C1073-300 occurred with the highest incidence among all other Corcept's sponsored studies; the study was discontinued early because of a high incidence of rash. Fifty subjects discontinued study because of rash; rash led to the study discontinuations in all treatment groups, including two placebo groups. The earliest discontinuation because of rash occurred on Day 4 after the subject received a total of three daily doses of study drug, and the latest discontinuation occurred on Day 14 after the subject received a total of 13 daily doses of study drug. The majority of patient discontinued study because of rash during the second week of the study (47/50 patients). The incidence of rash was highest in the mifepristone 1800 mg group (28/60 patients, 46.7%), followed by 600 mg group (15/45 patients, 33.3%), followed by placebo and moxifloxacin groups combined (9/ 90 patients, 10%). The rashes were treated with antihistamines and/or topical lotions when needed. The majority of rashes resolved within one to two weeks. Biopsies of rash tissue from eight subjects with rash revealed histological findings of typical simple drug exanthemas. A rechallenge study (Study 301) was designed to

explore mechanism of drug rash associated with mifepristone treatment; this study is discussed in details in Section 7.4.5. Briefly, of the five enrolled subjects who experienced drug rash during the Study 300, none experienced a drug rash that was confirmed by a dermatologist.

In Study Cl073-425four subjects of 30 enrolled subjects experienced rash and terminated study early because of this AE (dose of Korlym was 600 mg).

PK studies
Rash was occasionally reported in healthy subjects treated with mifepristone in PK studies. Seven subjects in Study C1073-23, three subjects in Study C1073-24, and three subjects in Study C1073-25 developed rash. Rash led to the study withdrawal in two subjects in Study C1073-27 (dose of mifepristone 1200 mg) and in three subjects in Study C1073-25 (dose of mifepristone 1200 mg).

Studies in other indications
Total of 29/ 782 (3.7%) mifepristone-treated patients and 11/ 584 (1.9%) placebo-treated patients developed rash in studies of mifepristone in patients with major depression (C1073-02, C1073-03, C1073-06, C1073-07, and C1073-09). In the five multi-dose studies rash has been reported in 10/127 (8%) subjects who received mifepristone (Studies 99-01 an 1073-04 in patients with major depression, C1073-05 in normal subjects and hepatically impaired, C1073-71 in Alzheimer's patients, C1073-200 in prevention of weight gain). Two SAEs of generalized rash with fever that led to hospitalization were reported in two subjects: one subject with major depression in Study CI073-06 (mifepristone 1200 mg) and one Alzheimer's dementia subject in Study C1073-71 (mifepristone 300 mg). The rash was reported as drug eruption in both cases.

Liver enzymes
Studies in Cushing's syndrome
Liver function tests were evaluated at screening visit, Day 14 and then at Weeks 6, 10, l6, 24, and at 6-Week follow-up visits in Study 400. In Study 415, laboratory tests were performed at every visit. In both studies changes from baseline in liver enzymes values were small and not clinically significant.

In Study 400, mean AlkPhos value decreased during the treatment with Korlym but returned to baseline value at 6-Week follow up visit, mean AST value increased to 29.4 U/l at Week 6 visit from 24 U/l at baseline and returned to the baseline values thereafter. Changes in LFTs reported as TEAEs in 2 patients each were the following: elevated LFTs, elevated ALT, and elevated AST (the Sponsor did not provide the information about the dose levels and whether these events occurred in the same or different patients).

Medical Officer comments:
There were findings of hepatotoxicity of mifepristone in chronic animal studies (refer to section4.3). The reported findings are of unknown significance in human, but Pharm. Tox reviewer recommend periodic monitoring of LFTs in patients chronically exposed to

Korlym. Thus, this reviewer further analyzed Study 400 datasets provided by The Sponsor. This analysis revealed the following findings:
1. Elevated AlkPhos levels
Two patients had elevated AlkPhos levels > 3 X ULN (# 06-003 and # 20-002). AST and ALT were normal in both patients. Elevated AlkPhos levels in these subjects were due to the underlying diseases in both patients and not to the drug. Patient # 06-003 had elevated AlkPhos and bilirubin at 6-Week follow-up visit due to amyloidosis. Patient #20-002 was diagnosed with neuroendocrine cancer with abdominal metastasis and had elevated AlkPhos at baseline and on Day 14 with normal levels of bilirubin. These subjects are described in details in Section 7.3.5.
2. Elevated AST and/or ALT levels
Two patients had elevated AST and/or ALT levels > 2 XUNL. Serum total bilirubin was within normal limits in both patients. Briefly:

- *Patient # 09-001 with Cushing's disease had transient elevation of ALT > 2 X ULN at Week 6 and 10 visits and > 3X UNL at Week 8 visit; AST was elevated of > 2 X ULN at Week 8 visit. ALT and AST normalized at Week 16 visit and remained normal thereafter. This patient had medical history of fatty liver prior to the study enrollment. No other information provided by the Sponsor*
- *Patient # 17-002 with Cushing's disease had a single elevation of ALT of > 2 X UNL at Day 14 visit, levels normalized thereafter. No other information provided by the Sponsor.*

3. All other subjects had occasional transient elevations in AST and/or ALT of < 2 X UNL, the degree of increase was inconsistent from visit to visit.

Overall, the LFTs abnormalities did not persist during the study, normalized without drug discontinuation and were observed in a few patients only. No conclusion about relationship of the observed LFT abnormalities with the study drug can be drawn at this time due to the limited information provided by the Sponsor and the only 6-month duration of the exposure. Longer exposure to the study drug might be required to detect clinically meaningful changes.

In Study 415, mean total bilirubin and alkaline phosphatase values increased significantly from 9.2 umol/L to 31.5 umol/L and from 118 U/Lto 1393 U/L at Month 12 visit, although median values remained unchanged. This increase in mean values reflects the abnormal increase in bilirubin and alkaline phosphatase levels in patient #06-003 due to amyloidosis; this event described in details in Section 7.3.1. Mean and median values for total bilirubin and alkaline phosphatase decreased at Month 18, and were lower than those at baseline. The increase in mean ALT and AST values observed at Month 18 is due to the elevation in ALT and AST values of > X3 UNL in one patient # 09-001 at Month 18 visit (last evaluation); the levels were normal during the previous visits. Patient's serum total bilirubin levels remained normal during all visits. The event was reported as AE related to the study drug; no other information provided by the Sponsor. This patient was treated with Korlym 1200 mg once a day, the dose was interrupted due to the event. Of note, the same patient had elevation in AST and ALT levels in Study 400 that normalized at the subsequent visits.

Studies in the prevention of weight gain

These were only studies were significant increase in liver enzymes was observed (studies C1073-200, C1073-200-1, and C1073-205):

- In Study C1073-200, three subjects discontinued the study because of elevated liver enzymes (all subjects received olanzapine plus 600 mg mifepristone). The occurrence of elevated liver enzymes was higher in the olanzapine plus placebo group (75%) than in the mifepristone plus olanzapine group (57%).
- In Study C1073-200-1, 17 subjects were withdrawn from the study because of the elevated LFTs (9 subjects received olanzapine + placebo, 8 received olanzapine + mifepristone). All subjects had LFTs elevation ≥ 5 times the upper limit of normal (ULN) or ≥ 3 times the ULN with a total bilirubin elevated above ULN. Total 20 / 54 subjects with at least one TEAE had LFTs elevation reported as AE, all subjects received olanzapine.
- In Study C1073-205, one subject discontinued study because of elevated transaminases. Total of two subjects had clinically significant elevated LFTs during the study. Both subjects received risperidone.

Overall, elevations in liver enzymes occurred in subjects who received olanzapine or risperidone; none of subjects who received mifepristone or placebo without antidepressants had elevation in liver enzymes; liver enzymes normalized in the majority of subjects at the follow-up visit. Abnormal liver function tests observed in these studies were most likely associated with the use of olanzapine or risperidone. Liver enzyme abnormalities are not unexpected AEs with the use of olanzapine or risperidone and are listed in olanzapine and risperidone labels.

Study 300 (TQT)

Elevations in liver enzymes were also observed in Study 300. In Part I Study 300, 7/15 subjects who received 1800 mg of mifepristone had a shift from normal at baseline to high at Day 14. In Part II of the study, 12 / 45 subjects who received 600 mg mifepristone and 25/ 60 subjects who received 1800 mg mifepristone had an abnormal LFT's. One of 45 subjects who received 600 mg of mifepristone had LFT's 3 x ULN. Of those who received 1800 mg of mifepristone, LFT's were ≥ 2 x ULN in 8 subjects, and ≥ 3 x ULN in three subjects. Values for both AST and ALT returned to near baseline levels at the follow-up visit.

Other non-Cushing's Corcept-sponsored studies

In all other studies no clinically significant changes in LFTs occurred. The Sponsor stated that in studies of patients with major depression some changes from baseline values occurred, but they were not clinically meaningful.

Fatigue, nausea and headache

The only other non-serious adverse events that were observed with increased frequency in overall Corcept's clinical program during mifepristone administration were fatigue, and gastrointestinal symptoms. These events are discussed in Section 7.4.1

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Incidence of common treatment-emergent adverse events (TEAEs)
Studies in patients with Cushing's syndrome
Overall, the profile of TEAEs in Cushing's studies including fatigue, headache and gastrointestinal symptoms was similar to the profile of AEs reported in the other Corcept-sponsored studies, in published literature and in the current label for Mifeprex. The frequency of nausea (48% and 27%) in the studies 400 and 415 was lower, and the frequency of headache (44% and 23%, respectively) was comparable to the frequency of these AEs reported already in Mifeprex label (61 % for the nausea and 31% for the headache, respectively). The fatigue was observed more frequently in patients with Cushing's syndrome (27%-48%) than reported in Mifeprex label (10%), most likely because of the longer exposure to Korlym in Cushing's syndrome trials. Many TEAEs including adrenal insufficiency, hypokaliema, hypertension, endometrial thickness and/or bleeding, elevated TSH are based on Korlym's mechanism of action and discussed in Section 7.3.5 in details.

Study 400 (Table 54)
All 50 patients (100%) experienced at least one adverse event during the study. The most frequent TEAEs were nausea and fatigue (24/50 (48%) of patients each followed by headache (22/50 (44%) patients) and decreased blood potassium (17/50 (34%) patients). 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. Four subjects reported worsening of Cushing's syndrome during the study; the Sponsor did not report the specific symptoms that were associated with the re-occurrence of the hypercortisolemia. Three of these four subjects had completed study drug dosing when the TEAE started, and had not taken Korlym for more than 2 weeks (Subjects # 06-003, 24-001, and 24-002). The fourth subject experienced a worsening of Cushing's syndrome that started the day after the last dose (Subject #24-004).
Hypertension occurred in 12 patients (24%) and was considered as drug related in 5 subjects (one subject in C-HT and 4 subjects in C-DM cohort). The Sponsor stated that hypertension was associated with hypokalemia in majority of patients suggesting apparent mineralocorticoid excess. Hypertension resolved in 6/12 subjects and was ongoing in the other six subjects after the study completion. There were six TEAEs of the exacerbation of autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, psoriasis, gout, and asthma; 4/6 TEAEs were graded as possibly related to study drug. Adrenal insufficiency was reported in two subjects (discussed in details in section 7.3.5). The Sponsor reported that 88% of subjects (44/50) experienced TEAEs that were considered related to study drug. The most frequent drug-related AEs (occurred in > 5 subjects) were fatigue, nausea, hypokalemia, headache, endometrial hypertrophy, decreased appetite, arthralgia, dry mouth, peripheral edema, myalgia, dizziness, vomiting, abnormal TFTs, and hypertension. Although the presented data is similar to the data reported in the Table 54, the frequency is based on the judgment of the individual

investigator, which may not be entirely bias-free and is subject to inconsistency between observers.

Medical Officer's comments:
1. Cushing's syndrome exacerbation
The worsening of Cushing's syndrome occurred in few patients only (4 patients) and after treatment discontinuation, thus, is most likely due to the treatment interruption, and not to the "escape" phenomenon. The small number of patients and relatively short duration of treatment do not allow the meaningful conclusion regarding the development of the "escape" phenomenon (Loriaux, 2001; Nieman, 2002), and longer observation might be required.
2. Worsening of hypertension
Worsening of hypertension was observed in 12 subjects receiving Korlym and is most likely due to the activation of mineralocorticoid receptors by high cortisol levels; hypertension was frequently associated with hypokalemia and edema. Of note, the control of hypercortisolemia-induced hypertension was one of the primary efficacy endpoints in the study. Thus, the control of hypertension might not be achieved and actually might worsen with Korlym treatment, because of the increased mineralocorticoid activity associated with high cortisol levels.
3. Exacerbation of autoimmune diseases
There were six AE of worsening underlying autoimmune disorders. Cortisol has immunosuppressive and anti-inflammatory properties, thus high levels of cortisol may mask the manifestation of the autoimmune disorders. Korlym, by blocking the glucocorticoid receptors and preventing biological action of cortisol, may exacerbate such disorders.

Seven subjects (14%) experience at least one mild TEAEs, and 18 subjects (36%) experienced at least one moderate TEAE. Twenty-five subjects (50%) experienced 52 severe events. The only severe TEAEs that occurred in more than two subjects each were fatigue (4 subjects), nausea and vomiting (3 subjects each). The other severe AEs were hypokalemia, dizziness, headache, somnolence, anxiety and respiratory failure and occurred in two subjects each. Twenty subjects (40.0%) experienced at least one TEAE that caused an interruption or reduction in study drug. The most frequent TEAEs that led to the interruption or reduction in study drug were nausea (6 subjects, 12.0%) and fatigue (4 subjects, 8.0%) followed by adrenal insufficiency, vomiting, pain, decreased appetite, headache, anxiety, and dyspnea that occurred in two subjects each.

Table 54. Summary of Treatment-emergent Adverse Events Occurring in > 5% Subjects in Study 400

System Organ Class / Preferred Term	**Overall n (%)**
Subjects with at least 1 TEAE	50 (100)
Gastrointestinal disorders	
Nausea	24 (48.0)
Vomiting	13 (26.0)
Dry mouth	9 (18.0)

Diarrhea	6 (12.0)
Constipation	5 (10.0)
Gastroesophageal reflux disease	4 (8.0)
Abdominal pain	3 (6.0)
General disorders and administration site conditions	
Fatigue	24 (48.0)
Edema peripheral	13 (26.0)
Pain	7 (14.0)
Asthenia	3 (6.0)
Malaise	3 (6.0)
Edema	3 (6.0)
Pitting edema	3 (6.0)
Thirst	3 (6.0)
Nervous system disorders	
Headache	22 (44.0)
Dizziness	11 (22.0)
Somnolence	5 (10.0)
Musculoskeletal and connective tissue disorder	
Arthralgia	15 (30.0)
Back pain	8 (16.0)
Myalgia	7 (14.0)
Pain in extremity	6 (12.0)
Muscular weakness	4 (8.0)
Flank pain	3 (6.0)
Musculoskeletal chest pain	3 (6.0)
Investigations	
Blood potassium decreased	17 (34.0)
Thyroid function test abnormal	9 (18.0)
Blood triglycerides increased	4 (8.0)
Skin and subcutaneous tissue disorders	
Dry skin	4 (8.0)
Ecchymosis	4 (8.0)
Acne	3 (6.0)
Infections and Infestations	
Sinusitis	7 (14.0)
Nasopharyngitis	6 (12.0)
Urinary tract infection	4 (8.0)
Upper respiratory tract infection	3 (6.0)
Metabolism and nutrition disorders	
Decreased appetite	10 (20.0)
Anorexia	5 (10.0)
Hypoglycemia	3 (6.0)
Vascular disorders	
Hypertension	12 (24.0)
Hot flush	3 (6.0)
Reproductive system and breast disorders	
Endometrial hypertrophy	10 (20.0)
Vaginal hemorrhage	4 (8.0)
Metrorrhagia	3 (6.0)
Respiratory, thoracic, and mediastinal disorders	
Dyspnea	8 (16.0)
Pharyngolaryngeal pain	4 (8.0)

Cough	3 (6.0)
Psychiatric disorders	
Anxiety	5 (10.0)
Insomnia	3 (6.0)
Eye disorders	
Vision blurred	4 (8.0)
Injury, poisoning, and procedural complications	
Contusion	3 (6.0)
Endocrine disorders	
Cushing's syndrome	4 (8.0)
Renal and urinary disorders	
Pollakiuria	3 (6.0)

Source: Sponsor's table 30, Module 5, Vol 31, CSR 400, p. 106-108, modified.

Other adverse events that were reported in 2 subjects each were: dyspepsia, chest discomfort, irritability, pyrexia, hypoesthesia, restless leg syndrome, tremor, musculoskeletal stiffness, rheumatoid arthritis, increased ALT, increased AST, abnormal LFTs, increased VLDL, increased weight, alopecia, hyperhidrosis, pruritus, rash, influenza, vulvovaginal mycotic infection, increased appetite, vitamin D deficiency, decreased lymphocytes, hypotension, respiratory failure, confusion, depression, foot fracture, gynecomastia, heart palpitations, anemia and tinnitus.

Study 415 (Table 55)
All 30 subjects enrolled in the study experienced TEAEs. The overall adverse event profile in Study 415 did not rise new safety concern with Korlym use; majority of AEs were related to the mechanism of action of Korlym (hyperkaliemia, hypertension, vaginal bleeding), or already listed in Mifeprex label (nausea, rash, headache). Moreover, AEs reported in the extension study were similar in type to those reported in the initial Study 400, although the overall incidence of the events was generally lower in the extension study. The TEAEs that occurred with highest incidence were decreased blood potassium (9/30 subjects, 30%), fatigue (8/30 subjects, 27%), nausea (8/30 subjects, 27%), headache (7/30 subjects, 23%) and hypertension (7/30 subjects, 23%). Four patients with Cushing's disease (# 06003, #24001, #24002, and #24004) had 5 events of relapse of Cushing's syndrome features that were reported as not-related to the study drug events; the events occurred during 6-Week follow-up period in Study 400 (after the completion of treatment with Korlym) but before re-initiation treatment with Korlym in Study 415. The events resolved with re-initiation of the treatment with Korlym in Study 415. The majority of all TEAEs were mild (4/30 subjects, 13%) to moderate (16/30 subjects, 53%) in severity.

Table 55. Treatment-emergent Adverse Events Occurring in Three (10%) or More Subjects by System Organ Class and Preferred Term (Safety Population) in Study 415

System Organ Class **Preferred Term**	**N=30** **n (%)**
Subjects with at least 1 TEAE	30 (100.0)
Gastrointestinal disorders	
Nausea	8 (26.7)
Vomiting	4 (13.3)
General disorders and administration site conditions	
Fatigue	8 (26.7)
Edema peripheral	5 (16.7)
Infections and infestations	
Nasopharyngitis	5 (16.7)
Investigations	
Blood potassium decreased	9 (30.0)
Thyroid function test abnormal	5 (16.7)
Blood cholesterol increased	3 (10.0)
Blood testosterone free increased	3 (10.0)
Blood testosterone increased	3 (10.0)
Musculoskeletal and connective tissue disorders	
Back pain	3 (10.0)
Nervous system disorders	
Headache	7 (23.3)
Dizziness	5 (16.7)
Psychiatric disorders	
Anxiety	4 (13.3)
Reproductive system and breast disorder	
Endometrial hypertrophy	6 (20)
Vaginal hemorrhage	3 (10)
Vascular disorder	
Hypertension	7 (23.3)

Source: Sponsor's table 6, 4-month update CSR 415, pp.28-29.

Non-Cushing's Corcept's studies

The overall frequency and profile of TEAEs that occurred in healthy volunteers, in patients with renal and liver impairment, in patients with major depression and with Alzheimer's disease and in patients who participated in the trials of prevention of weight gain was comparable to the profile of TEAEs observed in patients with Cushing's syndrome; up to 100% of patients experienced TEAEs in the these supportive trials. The most common AEs in other Corcept's studies were gastrointestinal (nausea, vomiting, diarrhea, constipation, abdominal pain), nervous system-related (headache, dizziness), in the general disorders category (fatigue), and skin-related (rash). The type of adverse events was related to the population enrolled in the study; psychiatric and nervous system adverse events were common

in studies in psychotic depression and Alzheimer's disease. The only TEAEs that were reported with increased frequency in the other supportive Corcept's studies

7.4.2 Laboratory Findings

7.4.2.1 Studies in Cushing's syndrome

Overall, the most frequently reported TEAEs related to the laboratory values in Study 400 and 415 were decreased potassium (17/50 patients, 34% and 9/30 patients, 30%, respectively) and increased TSH values (9/50 patients, 18% and 5/30 patients, 16.7%, respectively).

Hormone levels (ACTH, cortisol, and TFTs) in studies in Cushing's syndrome
Serum cortisol and adrenocorticotropic hormone (ACTH) were evaluated on Days 1, 14 and then at Weeks 6, 10, 16, 24, and follow-up visit in Study 400 and every 3 months and at 6 Week follow-up visit in Study 415. There were no new trends in serum cortisol and ACTH level changes. As expected form the mechanism of action of Korlym as a glucocorticoid receptor antagonist, ACTH and cortisol levels increase during treatment with Korlym in subjects with Cushing's syndrome.

Study 400
Mean ACTH values increased during Korlym treatment from 66.1 ng/L ± 66.0 ng/L at entry to the maximum value of 142.4 ± 124.8 ng/L at Week 10; the first rise in ACTH values was noticed at Day 14 visit (100.9 ± 82.3 ng/L). The ACTH values stabilized after Week 10 visit and returned to baseline values at Week 24. Levels of ACTH at baseline were greater in subjects with ectopic ACTH compared to the ACTH values in patients with Cushing's disease. In contrast, the increase in ACTH levels was greater in subjects with Cushing's disease most likely because of the reduced negative feedback by glucocorticoid receptor blockade and preserved responsiveness of pituitary tumors to high cortisol levels. In the 43 subjects with Cushing's disease, ACTH increased on average by 2- fold by Week 10, and urinary cortisol increased up to 7.70-fold at Week 24/ET. The changes in serum cortisol levels in the overall population of patients with Cushing's syndrome followed the same pattern as ACTH levels - they 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). The relative increase in cortisol levels among the groups of subjects based on etiology (Cushing's disease, ectopic ACTH, and adrenal carcinoma) was the similar. By the 6-Week follow-up visit, ACTH and serum and urinary cortisol levels had declined from the 24-Week values and were approaching baseline levels.

Study 415
Mean UFC levels increased from 2009 nmol/24 hrs to 5762 nmol/24 hrs (median: from 340 nmol/24 hrs (range 45-36365 nmol/24 hrs) to 421 nmol/24 hrs (range 350-26981 nmol/24 hrs)). ACTH values increased two-fold (range 0.67- to 5.5 fold) during Korlym treatment: from 71.6±52.9 ng/L at study entry to 135 ±66 ng/L at Month 3 visit (n=7) to 111.3 ± 47.7 ng/mL at visit A2 (n=11) in patients with Cushing's disease (n=28). The Sponsor stated that the rise in ACTH levels in patients with Cushing's disease occurred at Month 2 visit and did not progress further with continued treatment. In patients with ectopic ACTH-producing tumors ACTH increased from 308 ± 308 ng/L (n=3) at study entry visit to 1492 ± 2055 ng/L at visit A1 (n=3).

> *Medical Officer's comments:*
> *The mean urinary cortisol values are higher than median urinary cortisol values most likely because of three outliers: two subjects with ectopic Cushing's syndrome and one subject with Cushing's disease had extremely high values of cortisol at the beginning of the study and at the last visit (13010 and 29577, 13498 and 26981, 36365 and 64462 nmol/24 hrs, respectively), thus the distribution is skewed to the right.*

Changes in TFTs are discussed in details in the Section 7.3.5.

Hematology
No clinically significant trend in hematologic values was noted in any of the study.

Study 400
Mean and median leukocytes count, neutrophils count decreased slightly from entry visit to the last visit assessment and returned to baseline values at follow up visit. Mean and median total and absolute lymphocytes count and total monocytes increased throughout the study, but returned to the baseline values in 6 weeks after the last dose of the study drug. Changes in hematological parameters reported as AEs in 2 or more patients were observed in six patients: hemoglobin decreased, lymphocyte count decreased and anemia in 2 patients each (the Sponsor did not provide the information about the dose levels and whether these events occurred in the same or different patients). Overall, all these changes are not clinically meaningful due to small changes and small number of patients, but changes in leukocytes, neutrophils, lymphocytes and monocytes count may be indicative of the improvement in hypercortisolemia. Table 56 presents summary statistics for hematology values in Study 400, values that increased by the end of the are highlighted in blue, values that decreased by the end of the study are highlighted in yellow.

Table 56. Summary of Hematology Parameter Values (Study 400)

Parameter	Entry (n=50)	Day 14 (n=49)	Day 28 (n=45)	Week 6 (n=41)	Week 10 (n=38)	Week 16 (n=35)	Week 20 (n=33)	Week 24 (n=42)	6 Week f/u (n=39)
Hemoglobin, g/L Mean (SD) Median (Min, Max)	134 (16.5) 137 (89, 163)		132.6 (15.7) 136 (96, 159)	129 (15.5) 131(95,156)	132 (15) 133 (96,160)	129 (17.6) 130 (87, 170)	133 (13.2) 136 (104, 161)	130.6 (11.8) 130.5 (103, 154)	137 (14.6) 135(105, 163)
Hematocrit, % Mean (SD) Median (Min, Max)	0.407 (0.05) 0.4 (0.3, 0.5)		0.405 (0.05) 0.4 (0.3,0.5)	0.39 (0.05) 0.4 (0.3,0.5)	0.4 (0.05) 0.4 (0.3,0.5)	0.4 (0.05) 0.4(0.3,0.5)	0.4 (0.04) 0.4(0.3,0.5)	0.4 (0.03) 0.4 (0.3,0.5)	0.4 (0.04) 0.4 (0.3,0.5)
Red cell count,10^9L Mean (SD) Median (Min, Max)	4.5 (0.6) 4.5 (2.6, 3.8)		4.4 (0.6) 4.4 (2.6, 5.6)	4.3 (0.6) 4.4 (2.7,5.5)	4.5 (0.5) 4.5 (3.2, 5.4)	4.4 (0.6) 4.3 (3, 5.5)	4.6 (0.5) 4.6 (3, 5.6)	4.4 (0.4) 4.5 (3.5, 5.2)	4.6 (0.5) 4.6 (3.2,5.3)
White cell count, 10^9L Mean (SD) Median (Min, Max)	9.3 (2.9) 9.1 (4.7, 20)		8.1 (2.8) 7.4 (3.8, 15)	8 (2.8) 7.4 (3.8, 15)	7.5 (2.8) 7 (3.8, 16)	7.3 (3.1) 7 (2.1, 18)	6.82 (2.3) 6.2(2, 11.9)	7.7 (3) 7.5 (2.2, 18.8)	9.6 (2.8) 9.2 (5.2, 18)
Neutrophils, % Mean (SD) Median (Min, Max)	72.9 (7.8) 73.4 (51,92)		67.7 (8.7) 68.6 (47, 91)	68 (8.6) 68 (48, 87)	66 (9.4) 67.2 (46, 87)	64 (11.6) 65 (40, 88)	63.4 (9.4) 66 (44,88)	66.4 (10) 68.2 (44, 89)	73.3 (8.5) 73 (58, 95)
Neutrophils absolute, 10^9L Mean (SD) Median (Min, Max)	6.8 (2.3) 6.6(2.9, 14.5)	5.2 (1.6) 5,2 (2, 9)	5.5 (2.2) 4.8 (2.3, 11)	5.5 (2.2) 5.6 (2.3, 12)	5 (2.3) 4.5 (2.1, 12)	4.8 (2.5) 4.6(1.2*, 12)	4.4 (1.8) 4.1 (1.5*, 8)	5.2 (2.5) 5 (1.6*, 12.8)	7.1 (2.5) 7.2 (3.5, 15)
Lymphocytes, % Mean (SD) Median (Min, Max)	20.2 (7.2) 19 (7, 34)	23.8 (7.2) 25 (8, 42)	24 (7.2) 24 (7.3, 43)	23 (7.1) 23 (6.7, 42)	25.3 (8.5) 24 (4, 50)	27 (10.4) 26 (4, 55)	27.6 (8.4) 26 (9, 43)	25.7 (9.6) 24 (8.7, 45)	20.1 (7.7) 18.5 (2, 35)
Lymphocytes absolute, 10^9/L Mean (SD) Median (Min, Max)	1.8 (0.7) 1.7 (0.3, 3.8)	1.8 (0.7) 1.7(0.4, 3.7)	1.8 (0.7) 1.8 (0.4, 3.8)	1.8 (0.7) 1.7 (0.3, 4)	1.8 (0.7) 1.6 (0.3, 3.3)	1.8 (0.7) 1.8 (0.3, 4)	1.8 (0.7) 1.7 (0.2, 3.5)	1.9 (0.7) 1.7 (0.3,4.6)	1.9 (0.8) 1.8 (0.2, 5)
Monocytes, % Mean (SD) Median (Min, Max)	5.1 (2) 5.1 (0.7, 9)	5.9 (2.2) 5.5 (2,11)	6 (3) 5.6 (0, 14)	6.4 (2.4) 6.4 (2.7, 13)	6.2 (2.5) 5.8 (1, 14)	6.5 (3.3) 6 (2, 18.5)	6.4 (2.8) 6 (2, 16)	5.45 (2.5) 5.4 (1, 14)	4.3 (1.7) 4.3 (0.1, 9)
Monocytes absolute, % Mean (SD) Median (Min, Max)	0.5 (0.3) 0.4 (0.03,1.3)	0.5 (0.2) 0.5(0.2,1)	0.5 (0.3) 0.4 (0,1.4)	0.5 (0.2) 0.4 (0.2,1.4)	0.4 (0.2) 0.4 (0.1,1.1)	0.5 (0.3) 0.4(0.1,1.6)	0.4 (0.2) 0.4 (0.2,1)	0.4 (0.2) 0.4 (0.1,1)	0.4 (0.2) 0.4 (0.01, 1)
Platelets, 10^9/ L									

Mean (SD) Median (Min, Max)	253 (75.5) 253 (85, 491)	270 (76) 255 (103, 513)	305 (102) 287 (146, 566)	286 (89) 271 (170, 618)	292 (84) 278 (86, 528)	275 (78) 265 (95, 492)	284 (84) 266 (168, 496)	291 (82) 289 (154, 499)	282 (86) 269 (132, 553)

Source: Sponsor's table 14.3.5.1.1, Module 5, Vol 33, modified;
*Patient # 10-002 with ectopic Cushing's syndrome had low absolute neutrophils count (normal range 1.8 10^9/l) at Week 16 through Week 24 visit; the levels were normal at previous visits and normalized at 6-Week follow up visit..

Analysis focused on outliers or shifts from normal to abnormal did not raise any new safety concerns; the shift from normal to abnormal values occurred in only few patients, the changes were small and not clinically relevant.

Study 415

Mean and median leukocytes count and neutrophils count decreased slightly from entry visit to the last visit assessment. Mean and median platelets count decreased at Month 18. Mean and median total and absolute lymphocytes count and total monocytes count slightly increased at Month 18 visit. All these changes most likely are not clinically meaningful due to small changes and overall small number of patients evaluated at each visit, but may be also indicative of the improvement in hypercortisolemia (Table 57).

Table 57. Summary of Hematology Parameter Values (Study 415)

Parameter	Entry , n=30	Month 12, n=24	Month 18, n=6
Hemoglobin, g/L			
Mean (SD)	133.7 (14.6)	132.5 (18.13)	135.3 (11.20)
Median (Min, Max)	136 (104, 158)	139 (94, 164)	132 (126, 156)
Hematocrit, %			
Mean (SD)	0.407 (0.04195)	0.403 (0.051)	0.406 (0.034)
Median (Min, Max)	0.407 (0.32 ,0.48)	0.418 (0.3, 0.49)	0.405(0.37, 0.46)
Red cell count,10^9L			
Mean (SD)	4.53 (0.481)	4.48 (0.579)	4.52 (0.392)
Median (Min, Max)	4.50 (3.5, 5.2)	4.50 (3.2, 5.4)	4.55(4.1, 5.1)
White cell count, 10^9L			
Mean (SD)	9.18 (3.124)	7.03 (2.597)	6.37 (1. 08)
Median (Min, Max)	8.20 (5.2, 18.0)	6.75 (4.2, 14.2)	6.8 (4.6, 7.4)
Neutrophils, %			
Mean (SD)	72.55 (9.23)	66.07 (12.77)	59.40 (9.26)
Median (Min, Max)	72.5 (59.2, 95.0)	64.30 (45.3, 92.0)	59.35 (49.7,74.0)
Neutrophils absolute, 10^9L			
Mean (SD)	6.741 (2.67)	6.04 (3.99)	3.803 (1.01)
Median (Min, Max)	6.39 (3.22, 15.3)	4.52 (2.11, 17.01)	3.670 (2.73, 5.18)
Lymphocytes, %			
Mean (SD)	21.01 (7.77)	26.61 (11.29)	32.2 (9.06)
Median (Min, Max)	21.50 (2.1, 32.8)	27.40 (3.0, 46.4)	30.65 (18.4, 43.3)
Lymphocytes absolute, 10^9/L			
Mean (SD)	1.85 (0.82)	1.94 (0.687)	2.03 (0.601)
Median (Min, Max)	1. 75 (0.17, 4.88)	2.08 (0.57, 3.09)	2.16 (1.29, 2.90)
Monocytes, %			
Mean (SD)	4.61 (1.76)	5.78 (1.68)	5.68 (0.59)
Median (Min, Max)	4.5 (1.0, 9.3)	5.90(2.6, 9.0)	5.70 (4.9, 6.3)
Monocytes absolute, %			
Mean (SD)	0.413 (0.1810)	0.470 (0.2819)	0.362 (0.0697)
Median (Min, Max)	0.380 (0.07, 0.95)	0.410 (0.19, 1.48)	0.360 (0.24, 0.43)
Platelets, 10^9/L			
Mean (SD)	274.0 (94.66)	274.9 (110.01)	252.2 (71.28)
Median (Min, Max)	256 (132, 553)	259 (92, 616)	233 (175, 363)

Source: sponsor's table 14.3.4.1, vol4, 4-month Safety update; Values that increased by the end of the study are highlighted in blue, values that decreased by the end of the study are highlighted in yellow

Analysis focused on outliers or shifts from normal to abnormal did not raise any new safety concerns; the shift from normal to abnormal values occurred in only few patients, the changes were small and not clinically relevant.

Chemistry

Overall, no clinically meaningful changes in biochemical parameters were reported in any of the studies except for the changes in potassium levels. Potassium values decreased throughout the study as expected from the mineralocorticoid action caused by elevated cortisol levels. This event is discussed in details in Section 7.3.5. No clinically meaningful changes were observed in LFTs parameters (refer to Section 7.3.5).

Study 400

Mean and median BUN and glucose values decreased at the last study visit from the entry visit. Creatine levels slightly increased throughout the study but returned to the baseline value at 6-Week follow-up visit. Mean AlkPhos value decreased during the treatment with Korlym but returned to baseline value at 6-Week follow up visit. Mean AST value increased to 29.4 U/L at Week 6 visit from 24 U/L at baseline and returned to the baseline values thereafter. Mean glucose levels decreased during the treatment with Korlym; the decrease in glucose values is due to the diminished biological action of cortisol and discussed in details in Section 6.1.4. The largest decrease was observed at Week 16 visit; mean values decreased from 4.1 mmol/L at baseline to 3.8 mmol/L. Table 58 presents summary of biochemical data; values that increased by the last visit on the study are highlighted in blue; values that decreased are highlighted in yellow. Changes in chemistry parameters reported as AEs in 2 or more patients were the following: elevated LFT's, elevated ALT, elevated AST, LDL/HDL ratio increased, VLDL increased (2 patients each), hypoglycemia (3 patients) and elevated triglycerides (4 patients); the Sponsor did not provide further information about the dose levels and whether these events occurred in the same or different patients. The LFTs changes are discussed in Section 7. 3.5.

Table 58. Clinical Chemistry Parameter (Study 400)

	Entry (n=50)	**Day 14 (n=50)**	**Day 28 (n=44)**	**Week 6 (n=43)**	**Week 10 (n=37)**	**Week 16 (n=35)**	**Week 20 (n=31)**	**Week 24 (n=41)**	**6 Week f/u (n=40)**
Sodium, nmol/L Mean (SD) Median (Min, Max)	141 (2.6) 141 (134, 146)	143 (2.8) 142 (138, 152*)	142 (2.4) 142 (136, 147)	142 (2.48) 141 (137, 150*)	142 (2.4) 141 (137, 149)	142 (1.7) 142 (138, 145)	142 (2.5) 142 (136, 146)	141(2.3) 141(136, 146)	140 (1.2) 140 (136, 144)
Potassium, mmol/L Mean (SD) Median (Min, Max)	4.1 (0.3) 4.1 (3.2, 4.7)	4 (0.5) 4 (2.5, 5.2)	3.9 (0.5) 4 (3, 4.8)	3.9 (0.5) 4 (2.7, 4.7)	3.9 (0.5) 4 (2.9, 5.6)	3.8 (0.6) 3.8 (2.1, 5)	4.2 (0.7) 4.1 (2.9, 7)	4.0 (0.4) 4.1 (3, 5)	4.2 (0.5) 4.3 (2.5,5)
Chloride, mmol/L Mean (SD) Median (Min, Max)	104 (3.3) 104 (95, 110)	104 (3.5) 104 (92, 110)	104 (3.05) 104 (97, 111)	104 (3.6) 104 (93, 111)	104 (2.8) 104 (97, 110)	104 (3.2) 105 (93, 109)	104 (3.01) 104 (97, 109)	104(3.2) 105 (95, 113)	103 (3.7) 103 (88, 108)
CO2 , mmol/L Mean (SD) Median (Min, Max)	23.7 (3.2) 23 (16, 34)	25.7 (3.1) 25.5 (21, 34)	25.4 (2.6) 25.5 (21, 33)	24.5 (3.5) 24 (17, 33)	24.4 (3.02) 24 (17, 33)	24.5 (3.2) 24 (17, 37)	25.4 (3.7) 25 (15, 34)	24 (2.8) 23 (17, 31)	24.8 (3. 2) 25 (17, 33)
BUN, mmol/L Mean (SD) Median (Min, Max)	5.5 (1.8) 5.5 (2, 10.5)	4.3 (1.3) 4.2 (2, 8)	4.2 (1.5) 4.5 (2, 8)	4.2 (1.9) 4 (2, 11)	4.5 (1.8) 4.5 (2, 10)	4.3 (1.8) 3.5 (2, 9)	4.5 (1.5) 4.5 (2, 8)	4.8 (1.6) 4.5(2,10	6.4 (1.9) 6.2 (2, 12)
Creatinine, umol/L Mean (SD) Median	75.6 (16.7)	78.4 (17) 71(44, 133)	83.5 (19.5)	82 (23) 80 (44,	86 (25) 80 (53,	84 (23) 80(53,	86 (17.8) 88 (53,	83(20.8) 80(53,	77 (18.9) 71 (44,

(Min, Max)	71 (44, 115)		80 (53, 133)	150)	159)	159)	133)	168)	141)
Glucose, mmol/L Mean (SD) Median (Min, Max)	6.7 (3.5) 5.3 (3.1, 18.8)	6.2 (2.2) 5.4 (4, 15)	6 (3) 5.3 (3.5, 24)	5.8 (2.1) 4.9 (3.2, 14)	5.6 (1.6) 5.1 (4.1, 11)	5.4 (1.4) 4.9 (4, 10)	5.6 (1.3) 5.1(4.4,10)	5.4 (1.6) 5(4, 13.2)	
Bilirubin total, umol/L Mean (SD) Median (Min, Max)	8.7 (4.3) 6 (4, 22)	9.2 (4.7) 8 (4, 28)		9.5 (5.1) 8 (4, 26)	9.8 (5.4) 8 (4, 24)			9.1 (4.8) 8 (4, 30)	9.3 (5.2) 8 (4, 30)
AST, U/L Mean (SD) Median (Min, Max)	24 (11.6) 21 (11, 74)	25.3 (10.5) 22 (12, 54)		29.4 (15.9) 24 (12, 85)	25.2 (13.2) 21.5 (12, 73)	22.4 (10.8) 20.5 (9, 75)		20.9 (8) 19(9, 62)	20.8 (8) 19 (9,50)
ALT, U/L Mean (SD) Median (Min, Max)	32. 6 (23) 29 (10, 157)	29 (16.2) 25.5(9, 102)		31. 6 (22.7) 24 (11, 129)	26.9 (21.2) 20 (8, 124)	32. 6 (23) 19 (80, 172**)		19 (9.2) 16 (7,54)	26.7 (12.2) 25 (11, 61)
AlkPhos, U/L Mean (SD) Median (Min, Max)	101.6 (87.4) 88.5 (48, 663^)	85.5 (46.9) 75 (43, 324^)		76.5 (33.5) 69 (43, 214)	76 22.4) 70 (47, 135)	83 (32.3) 73(43, 176)		84(28.7) 76(48, 185)	112 (74.5) 98 (59,515)

Source: Sponsor's table 14.3.5.1.2, Module 5, Vol 33, modified
*Patient # 01-001, 18-001, and 20-002 had elevated sodium level: patient # 01-001 had concomitant diabetes insipidus, patient # 18-001 had concomitant diabetes and congestive heart failure, patient #20-002 had renal insufficiency. No other information is provided by the Sponsor; the sodium levels normalized in all patients at the subsequent visits
** Patient # 09-001 had normal total bilirubin levels and transient elevation in ALT and AST of > 2 XUNL, levels normalized at the subsequent visits (refer to Section 7.3.5)
^ Patient #20-002 had elevated AlkPhos levels at baseline and subsequent visit due to the neuroendocrine tumor with abdominal metastasis (refer to Section 7.3.5).
^^Patient # 06-003 had elevated AlkPhos levels at follow up visit due to amyloidosis (refer to Section 7.3.5)

Analysis focused on outliers or shifts from normal to abnormal did not raise any new safety concerns; the shift from normal to abnormal values occurred in only few patients, the changes were small and not clinically relevant.

Study 415

Mean and median BUN and glucose values slightly decreased at the last visit assessment from entry visit; no episodes of hypoglycemia and no glucose levels < 2.9 mmol/L (52 mg/dl) were reported in any of the patients. Creatine levels slightly increased at Month 6 and 12 visits, but than returned to the baseline value. The largest decrease in mean potassium levels was observed by Month 6; the mean levels returned to the baseline values at Month 15 visit (refer to Section 7.3.5 for the further discussion of hypokalemia events).
Changes in LFTs are discussed in details in Section 7.3.5. Briefly, mean total bilirubin and alkaline phosphatase values increased significantly from 9.2 umol/L to 31.5 umol/L and from

118 U/L to 1393 U/L at Month 12 visit, although median values remained unchanged. Mean and median values for total bilirubin and alkaline phosphatase decreased at Month 18, and were lower than those at baseline. The increase in mean ALT and AST values was observed at Month 18. All changes in mean LFTs values reflect the abnormal values reported in two patients # 09-001 and #06-003. Patient # 09-001 had elevation in AST and ALT levels and normal serum total bilirubin level at the last study visit; no other information was provided by the Sponsor. Patient # 06-003 had elevation in AlkPhos levels due to the amyloidosis. These events are described in details in Section 7.3.5.

Table 59 presents summary of biochemical data; values that increased by the last visit on the study are highlighted in blue; values that decreased are highlighted in yellow.

Table 59. Clinical Chemistry Parameter (Study 415)

Parameter	**Entry**	**Month 6, N=25**	**Month 12, N=20**	**Month 15, N=12**	**Month 18, N=6**
Sodium (mmol/L)	N=30				
Mean (SD)	140.7 (2.01)	142.2 (2.58)	141.8 (2.86)	141.7 (2.31)	
Median (Min, Max)	141 (136, 144)	142 (137, 149)	142 (135, 148)	141 (139, 145)	
Potassium (mmol/L)	N=30				
Mean (SD)	4.20 (0.564)	4.04 (0.492)	4.13 (0.473)	4.23 (0.408)	
Median (Min, Max)	4.30 (2.5, 5.0)	4.10 (3.1, 5.2)	4.05(3.4, 5.2)	4.25 (3.5, 4.9)	
Chloride (mmol/L)	N=30				
Mean (SD)	103.3 (4.37)	104.2 (3.17)	104.7 (4.74)	103.9 (2.47)	
Median (Min, Max)	104 (88, 110)	105 (95, 109)	104 (94, 119)	105 (100, 108)	
CO2 (mmol/L)	N=30				
Mean (SD)	25.0 (2.99)	25.4 (2.87)	23.9 (4.70)	24.4 (2.07)	24.2 (1.47)
Median (Min, Max)	25 (20, 33)	25 (21, 32)	24 (7*, 31)	25 (21, 27)	25 (22, 26)
BUN, (mmol/L)	N=30				
Mean (SD)	6.42 (2.035)	5.12 (1.883)	6.43 (4.420)	5.08 (2.054)	4.92 (1.158)
Median (Min, Max)	6.0 (3.5, 12.5)	4.50 (2.0, 9.0)	4.75 (2.0, 22.0)	4.50(2.5, 9.0)	4.75 (3.5, 7.0)
Creatinine, (umol/L)	N=30				
Mean (SD)	77.3 (20.79)	82.8 (22.25)	85.0 (27.21)	78.1 (18.66)	78.0 (21.83)
Median (Min, Max)	71 (53, 141^)	80 (53, 150^)	80 (53,177*)	76 (53, 106)	75 (53, 106)
Glucose (mmol/L)	N=27				
Mean (SD)	6.04 (3.453)	5.71 (3.062)	6.08 (2.312)	5.61 (1.651)	5.55 (2.825)
Median (Min, Max)	4.80 (4, 18.9)	4.9 (2.9, 18.1)	5.40 (3.6, 12.7)	5.15 (3.7,10.2)	4.45 (4.2, 11.3)
Bilirubin total (mmol/L) ,	N=29				
Mean (SD)	9.2 (5.28)	10.6 (6.26)	31.5 (104.19)	8.2 (3.46)	8.0 (2.53)
Median (Min, Max)	8 (4, 30)	8 (6, 32)	8 (4, 474)	6 (6, 16)	7 (6, 12)
AST (U/L)	N=29				
Mean (SD)	19.9 (9.22)	20.1 (7.55)	22.7 (19.00)	21.0 (9.66)	48.8 (76.08)
Median (Min, Max)	18 (9, 56)	19 (11, 47)	18 (12, 100)	19 (14, 49)	19 (13, 204)
ALT (U/L),	N=29				
Mean (SD)	26.2 (11.31)	19.2 (8.57)	19.2 (9.71)	23.0 (14.03)	54.3 (88.61)
Median (Min, Max)	24 (12, 56)	18 (7, 48)	16 (3, 47)	17 (13, 61)	19 (12, 235)
Alkaline Phosphatase (U/L)	N=29				
Mean (SD)	118.2 (85.50)	89.7 (30.68)	153.0 (293.48)	88.4 (33.41)	75.5 (31.07)
Median (Min, Max)	99 (59, 515)	76 (54, 182)	92 (46, 1393)	82 (52, 158)	63 (53, 135)

Source: Sponsor's table 14.3.4.2, Module 5, Section 5.3.5.2.2
* Patient 06-003 had low CO2 and high creatinine levels due to renal failure; this patient was diagnosed with amyloidosis and died due to the progression of the disease (refer to Section 7.3.1).
^Patient # 10-004 had elevated creatinine levels of 141 umol/L at study entry, the levels increased to 177 umol/L at Month 1 visit, and decreased to 150 umol/L at Month 6 visit, no other information is provided by the Sponsor. This patient also had medical history of chronic renal insufficiency and elevated creatinine levels up to 168 umol/L in Study 400.

Analysis focused on outliers or shifts from normal to abnormal did not raise any new safety concerns; the shift from normal to abnormal values occurred in only few patients, the changes were small in the majority of the patients and not clinically relevant.

Lipids

Decline in HDL-cholesterol and total cholesterol levels was common during treatment with Korlym in both studies and resolved on cessation of Korlym treatment.
The changes in HDL levels in patients with Cushing's syndrome are discussed in Section 7.3.5.

Study 400

The largest mean reduction in total cholesterol occurred at the end of the study visit and in the HDL levels at Week 6 visit (the levels decreased by 0.576 ± 0.9165 mmol/L and 0.470 ±0.5381 mmol/L, respectively). At 6-Week follow-up visit, HDL-cholesterol levels returned to their baseline levels; the cholesterol levels remained lower compared to baseline levels. No analysis of lipid values based on the shift from normal to abnormal is performed by the Sponsor. Table 60 presents summary statistics for lipid values, values that decreased at the subsequent visit are highlighted in yellow.
Table 60. Summary of Lipid Data (Study 400; Safety Population)

Visit				Triglycerides (mmol/L)
	Total Cholesterol (mmol/L)	HDL-cholesterol (mmol/L)	LDL-cholesterol (mmol/L)	
Normal range	**< 5.1**	**> 0.88**	**0.00 – 3.35**	**< 2.3**
Baseline, n	46	46	44	46
Mean (SD)	5.611 (1.1992)	1.614 (0.7188)	3.097 (1.0273)	2.020 (1.1866)
Median	5.525	1.475	3.025	1.680
Min, Max	3.55, 8.70	0.65, 4.70	1.35, 5.70	0.64, 7.24
Week 6, n	43	43	40	43
Mean (SD)	5.003 (1.1209)	1.099 (0.4327)	2.841 (0.9792)	2.325 (1.0394)
Median	5.250	1.050	3.050	2.120
Min, Max	2.35, 6.95	0.40, 2.55	0.70, 4.70	0.70, 5.10
Week 6 change from baseline n	40	40	36	40
Mean (SD)	-0.510 (0.9824)	-0.470 (0.5381)	-0.085 (0.7956)	0.209 (1.2080)
Median	-0.350	-0.425	-0.025	0.290
Min, Max	-2.85, 1.35	-3.10, 0.75	-2.20, 1.80	-3.48, 3.38
Week 16 n	35	35	34	35
Mean (SD)	4.886 (1.1860)	1.071 (0.3808)	2.829 (1.0459)	2.081 (0.9663)
Median	4.750	1.050	2.800	1.880

Min, Max	2.70, 7.35	0.20, 2.10	1.00, 5.25	0.74, 5.22
Week 24/ET n	40	40	40	40
Mean (SD)	4.869 (1.1323)	1.108 (0.3121)	2.888 (0.9854)	1.907 (0.7248)
Median	4.700	1.100	2.850	1.820
Min, Max	2.65, 7.30	-0.50, 2.10	1.20, 5.20	0.74, 3.72
Week 24/ET change from baseline n	36	36	36	36
Mean (SD)	-0.576 (0.9165)	-0.368 (0.3076)	-0.208 (0.7076)	-0.001 (0.9285)
Median	-0.500	0.300	0.150	-0.040
Min, Max	-2.65, 1.05	-0.95, 0.10	-1.55, 0.90	-1.88, 2.00
6-Week follow-up n	23	23	23	23
Mean (SD)	5.391 (1.0783)	1.600 (0.4299)	2.941 (1.0064)	1.847 (0.9224)
Median	5.500	1.650	2.750	1.720
Min, Max	3.60, 7.15	0.90, 2.65	1.25, 4.70	0.68, 4.50

Source: Sponsor's table 34, Module 5, Vol 31, CSR 400, p. 136-137, modified.

Study 415

Mean reduction in HDL values from baseline was 0.37 mmol/L, 0.22 mmol/L and 0.37 mmol/L by Month 6, 12 and 18, respectively. The overall observed changes in HDL values were consistent with the overall trend of HDL decrease during treatment with Korlym (refer to Section 7.3.5). Mean and median total cholesterol levels decreased slightly by Month 6, but increased by Month 18. Mean and median LDL values increased slightly from baseline to the Month 18 visit. Table 61 presents summary statistics for lipid values; values that increased at the subsequent visit as compared to baseline visit are highlighted in blue, values that decreased at the subsequent visit as compared to baseline visit are highlighted in yellow.

Table 61. Summary of Lipids Values (Study 415)

	Entry (n=30)	**Month 6 (n=25)**	**Month 12 (n=20)**	**Month 18 (n=5)**
Total cholesterol (mmol/L):				
Mean (SD)	5.178 (1.03)	4.66 (1.08)	4.75 (1.2)	5.43 (0.3)
Median (Min, Max)	5.42 (3.05, 6.65)	4.65 (2.8, 6.7)	4.7 (2.95, 6.85)	1.3 (5.25, 5.95)
Change from baseline				
Mean (SD)		-0.35 (0.8)	-0.5 (0.96)	-0.17 (0.81)
Median (Min, Max)		-0.25 (-2; 1)	-0.45 (-3.5, 0.75)	-0.45 (-0.95, 1.2)
HDL (mmol/L)				
Mean (SD)	1.55 (0.45)	1.17 (0.36)	1.23 (0.51)	1.15 (0.3)
Median (Min, Max)	1.42 (0.74, 2.9)	1.1 (0.55, 1.8)	1.17 (0.15, 2.2)	1.1 (0.75, 1.6)
Change from baseline				
Mean (SD)		-0.37 (0.3)	-0.22 (0.26)	-0.37 (0.29)
Median (Min, Max)		-0.3 (1, 0.1)	-0.25 (-0.8, 0.25)	-0.3 (-0.85, -0.1)
LDL (mmol/L)				
Mean (SD)	2.94 (0.96)	2.72 (1.0)	2.83 (0.96)	1.62 (0.75)
Median (Min, Max)	3.04 (1.21, 4.75)	2.65 (1.0, 4.49)	2.72 (1.2, 4.46)	1.46 (0.9, 2.8)
Change from baseline				
Mean (SD)		-0.072 (0.66)	-0.34 (0.73)	0.2 (0.57)
Median (Min, Max		-0.06 (-1.45, 0.8)	-0.37 (-2.2, 0.82)	-0.08 (-0.26, 1.14)

Source: Sponsor's table 14.3.4.9, Module 5, Vol 4, 4-month Safety Update, modified.

Analysis focused on outliers or shifts from normal to abnormal did not raise any new safety concerns.

Laboratory findings in non-Cushing's studies
No clinically meaningful changes in serum hematology and chemistry values were reported in other Corcept-sponsored studies.

PK studies and studies in patients with Alzheimer's disease
In these studies some subjects had a shift in serum chemistry and hematology laboratory values from normal to high or low values. The Sponsor considered those changes as not clinically meaningful and all values returned to baseline levels at the time of the final assessments.

Studies in patients with major depression
There were four studies (C1073-02, C1073-03, C1073-06, and C1073-09) in which statistically significant changes in serum chemistry or hematologic values from baseline were seen. Overall, even though these changes were statistically significant, they were not clinically meaningful. These changes were as follows:

- Study C1073-02

Statistically significant changes in subjects who received mifepristone as compared to subjects who received placebo included mean decrease from baseline to Day 7 in total protein, potassium cholesterol; mean increases in sodium and chloride. ALT increased and bilirubin decreased in subjects who received mifepristone from baseline to Day 28.

- Study C1073-03

The changes in mean basophil, in mean neutrophils counts (decreases in both treatment groups), lymphocytes (increases in both treatment groups) at Day 7, mean platelet counts at Day 28 were statistically significantly different in patients who received mifepristone as compared with patients who received placebo. Mean ALT, albumin, BUN, bicarbonate, calcium, cholesterol, creatinine, potassium, sodium, T3, total protein, triglycerides, and uric acid at Day 7 and triglycerides at Day 28were statistically significantly different between the two treatment groups. Changes from baseline to Day 7 in albumin, total bilirubin, calcium, potassium, total protein, and uric acid (all decreased in both treatment groups); Alk Phos, ALT, BUN, cholesterol, and T4 (decreased in the mifepristone group and increased in the placebo group); and bicarbonate, creatinine, direct bilirubin, and sodium (increased in the mifepristone group and decreased in the placebo group) were statistically different between the two treatment groups.

- Study C1073-06

Changes in alkaline phosphatase, potassium, total T4, white blood cell count were statistically significantly different in patients who received mifepristone from patients who received placebo.

- Study C1073-09

Changes in erythrocytes, hemoglobin, sodium, potassium, chloride, calcium, creatinine, BUN, uric acid, albumin, total protein, cholesterol, AST, ALT, alkaline phosphatase at Day 7 visit were statistically significantly different in patients who received mifepristone from patients

who received placebo. The study results were submitted as abbreviated reports; no actual values for the laboratory parameters were provided.

Studies of Prevention of Weight Gain
Abnormal liver function tests (ALT, AST, and total bilirubin) were observed in all three studies (C1073-200-1, C1073-200, C1073-205) and were most likely associated with the use of olanzapine or risperidone. Elevations in liver enzymes occurred in subjects who received olanzapine or risperidone; none of subjects who received mifepristone or placebo without antidepressants had elevation in liver enzymes. Liver enzymes normalized in the majority of subjects at the follow-up visit. These findings are discussed in details in Section 7.3. 5.

7.4.3 Vital Signs

Studies in Cushing's syndrome
Measurements of weight, systolic and diastolic blood pressure, heart rate were reviewed. Overall, there was no evidence to suggest a clinically meaningful change in heart rate or body temperature in both studies (400 and 415).

Study 400
Changes in DBP and SBP and weight changes were efficacy endpoints in Study 400 and are discussed in sections 6.1.4 and 6.1.5. Mean heart rate was 77 ± 16 beats per minute at baseline (median 74, range 55-121) and varied from 79 ± 16 (median 76, range 50-120) at Day 7 visit to 71 ±11.7 (median 71.5, range 54-100) at 6-Week follow up visit. Vital signs abnormalities reported as AEs were: palpitations (2 patients), pyrexia (2 patients), hypotension (2 patients) and hypertension (12 subjects); no further information regarding these AEs is provided. Hypertension was most likely due to the mineralocorticoid action of elevated cortisol levels. No subjects discontinued the study due to the vital signs abnormalities. No analysis focused on shifts from normal to abnormal values is presented by the Sponsor.

Study 415
The mean and median systolic and diastolic blood pressure slightly increased by Month 6 visit. There was a mild increase in mean and median heart rate at Month 6 and 12 visits. These changes reflect the increase in maximum observed value in patient #06-003 who was diagnosed with amyloidosis and had multiple complications due to the disease progression (refer to Section 7.3.1). The mean and median weight increased by Month 12 visit, but than decreased to baseline value at Month 18 visit. No subjects discontinued the studies due to vital signs abnormalities. Analysis focused on shifts from normal to abnormal values demonstrated that four patients with normal diastolic blood pressure at baseline had elevated diastolic blood pressure at the last evaluation in the study; no other information is provided by the Sponsor. . Overall, the changes in DBP were small and most likely not clinically significant; no conclusion can be drawn at this time due to the limited information provided by the Sponsor, single measurements of the BP in individual patients, large variations in BP values during the previous visits, and/or introduction of the antihypertensive medications. Table 62 presents summary statistics for diastolic, systolic blood pressure, heart rate and weight values.

Table 62. Summary Statistics for Vital Signs values (Study 415)

Parameter	Entry, n=29	Month 6, n=22	Month 12, n=18	Month 18, n=5
Systolic BP (mmHg)				
Mean (SD)	129.4 (19.43)	135 (16, 52)	126.7 (18.8)	139 (23.69)
Median (Min, Max)	124 (96, 182)	130 (118, 180)	125 (99, 176)	130 (123, 180)
Diastolic BP (mm Hg)				
Mean (SD)	81 (13.13)	85 (9.13)	80.1 (13.58)	82.4 (5.9)
Median (Min, Max)	80 (57, 123)	87.5 (68, 108)	77.5 (63, 118)	84 (75, 90)
Heart rate (bpm)				
Mean (SD)	69 (9.15)	73.7 (10.2)	74 (14.1)	61 (9.26)
Median (Min, Max)	69 (54, 88)	73 (60, 92)	71 (56, 108)	60 (51, 76)
Weight (kg)				
Mean (SD)	98.1 (30.1)	97 (34.5)	104 (35.7)	98.02 (29.31)
Median (Min, Max)	88.2 (51 , 177)	90.9 (47.3, 185)	101 (50, 189)	107.7 (60.9, 136)

Source: Sponsor's table 14.3.6.1, Module 5, Volume 4, 4-Month safety update.

Non-Cushing's studies

Small, not-clinically meaningful changes in mean systolic and diastolic blood pressure, pulse rate, body temperature, and respiratory rate from baseline through discharge were reported by the Sponsor in Study 300. In Study 425 mean weight increased slightly from baseline in the mifepristone group but returned to baseline measurements by Day 84.

No clinically significant findings in vital signs were observed in PK food effect and drug interaction studies. One subject in Study Cl073-20 developed a mild TEAE of fever that was considered drug-related after receiving a single dose of 1200 mg mifepristone in the fasted condition; this resolved after treatment with ibuprofen. No clinically meaningful vital signs findings in PK studies in subjects with hepatic and renal impairment were reported. One subject with renal impairment developed TEAE of orthostatic hypotension (dose 600 mg/day) that was considered possibly related to the study drug; the event resolved without treatment next day.

In studies in subjects with major depression, there were few reports of changes in vital signs, the majority were considered not related to study medication. In Study C1073-02, vital signs and ECG findings reported as drug-related TEAEs included pyrexia and tachycardia in the mifepristone group. No other clinically relevant changes were found in these studies.

There were no significant findings in vital signs in studies of the prevention of weight gain (C1073-200, CL073-200-1, or C1073-205).

7.4.4 Electrocardiograms (ECGs)

The ECG results in patients with Cushing's syndrome and in other Corcept's safety supportive studies, including the results of TQT Study (Study 300) are discussed in sections 7.3.5 and 7.4.5, respectively.

7.4.5 Special Safety Studies/Clinical Trials

7.4.5.1 Study C1073-300 (Study 300): A Thorough ECG Trial Comparing Mifepristone and Placebo.

Data from the chronic toxicity safety study in dogs suggest that mifepristone might have an effect on cardiac repolarization; therefore Study 300 was conducted as a thorough ECG trial. Design and results of Study 300 were reviewed by Interdisciplinary Review Team for QT Studies on October 21, 2011; please refer to this review for the details. The study will be discussed in this section only briefly.

Primary end-point
The time matched difference to placebo in change from average baseline to day 7 in QTc based on an individual correction method for heart rate (ΔΔQTcI) after administration of a therapeutic (600 mg/day) and a supratherapeutic (1800 mg/day) doses of mifepristone.

Secondary end-point
QTc with Fridericia correction method, QTc with Bazett correction method, heart rate, PR, QRS, uncorrected QT interval, change in ECG morphological patterns, and correlation between the QTc and plasma concentrations of mifepristone and its three metabolites.

Safety end-points
Adverse events, changes in laboratory parameters, orthostatic vital signs and endocrinology safety (any manifestation of any adrenal insufficiency).

Design
This was a Phase 1 study of safety and tolerability and ECG effects of mifepristone in healthy volunteers. This study was conducted in two parts: Part I and Part 2. Part 1 was an open-label study assessing tolerability of supratherapeutic doses of mifepristone in healthy male subjects. Fifteen healthy males received 1800 mg of mifepristone daily for 14 days and were followed for safety by evaluation of AEs and clinical laboratory parameters for up to 43 days.
Part 2 (Thorough ECG Study or TQT Study) was double-blind (except for the use of moxifloxacin that was single blind), randomized, single-site, four-arm parallel study in healthy male subjects. In Part 2, all subjects were randomly assigned to the four treatment groups to receive either of two doses of mifepristone (600 or 1800 mg), placebo or placebo followed by a single dose of moxifloxacin (used as a positive control) administered on Day 14. The duration of each treatment was 14 days. In part I and II of the study ECG was performed at the screening visit, on Days 1, 5, 7, and 14; the ECG was recorded multiple times up to 23.5 hours on each day. Blood samples for PK analysis were collected on Day 1 (2 hours before the first dose), on Days 10 and 12 (trough samples), and on Days 7 and 14 at multiple time points up to 23.5 hrs post-dose. ECGs were evaluated by a central ECG laboratory, which was blinded to subject's treatment assignment. If subject experienced a rash, laboratory tests, including alpha-1-acid glycoprotein and CBC were performed and the subject was referred to a dermatologist

for further evaluation. Punch biopsies of an affected area of skin and normal-appearing skin were taken in the first 12 patients who developed rash in each treatment group.

Treatment Groups:
All subjects were randomized to the four treatment groups (in 1: 1: 1: 1 ratio) to receive one of four treatment regimens for 14 days:

- Placebo once a day
- Placebo once a day plus a single dose of moxifloxacin 400 mg on Day 14
- Mifepristone 600 mg once a day
- Mifepristone 1800 mg once a day.

Statistical analysis
The primary analysis was performed on day 7 because of the significant drop-out proportion of subjects due to the AEs between day 7 and day 14 of the dosing. The Sponsor indicated that this change in analysis is supported by similar exposure levels to the study drug and its metabolites on Day 7 as compared to Day 14. The PK parameters of mifepristone for Part I (on Days 7 and 14) and Part II (on Day 14 only) included C_{max}, T_{max}, t1/2 and AUC_{0-24} and were analyzed by descriptive statistics tabulated by treatment groups. Bioequivalence testing was done at the 1800 mg/day dose level to compare PK parameters between study Parts II versus I and between study days 14 versus 7. Safety data, including adverse event reports and results of laboratory tests, physical examinations, safety ECG monitoring, and vital sign assessments were summarized and analyzed by descriptive statistics.

Results
Patient Population and disposition
Two hundred forty healthy male volunteers, 18 - 45 years old were planned to be enrolled in the study and 195 healthy adult males were enrolled in this study (15 subjects - in Part 1 and 180 subjects - in Part 2). One hundred thirty eight subjects completed the study. The study was terminated prematurely because of an unexpectedly high frequency of AEs. Forty five patients received placebo, 45 patients received placebo with moxifloxacin, 45 patients received mifepristone 600 mg, and 60 patients received 1800 mg of mifepristone (Parts 1 and 2 were pooled).

Results of thorough ECG analysis
Interdisciplinary Review Team for QT Studies concluded that the thorough QT Study (TQT) is inconclusive. The assay sensitivity was not established, as the largest lower bound of the two-sided 90% confidence interval (CI) for the placebo adjusted, baseline-corrected QTcI ($\Delta\Delta$QTcI) for moxifloxacin was less than 5 msec. Therefore, small increase in QTc interval cannot be ruled out under the therapeutic dose of 600 mg, even though the observed upper bound of 90% two-sided confidence interval for the largest QTc interval change is less than 10 ms. In addition, the upper bound of two-sided 90% confidence interval for the largest QTc interval change is greater than 10 ms under supratherapeutic dose. The QT-IRT reviewer also concluded, that "the supratherapeutic dose (1800 mg) produces mean Cmax values 20% higher than the mean Cmax for the therapeutic dose (600 mg) at steady-state. These concentrations

are similar to those for the predicted worst case scenario (1200-mg dose in patients with mild renal impairment). At these concentrations there is no detectable relationship between mifepristone exposure and the ΔΔQTcI-interval. However, there is a dose-dependent increase observed in the response at steady-state. It is likely that the response has reached a plateau and ΔΔQTcI-interval prolongation is not anticipated at higher exposures". The reviewer agreed with the Sponsor's proposed language in the label regarding QT prolongation, but suggested that no study description should be included in the label. Overall summary of findings for analysis on Day 7 data is presented in Table 63.

Table 63. The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for mifepristone (600 mg and 1800 mg, Day 7) and the Largest Lower Bound for Moxifloxacin (Day 14) (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
Mifepristone 600 mg	12	4.2	(-0.4, 8.8)
Mifepristone 1800 mg	12	7.4	(2.8, 12.0)
Moxifloxacin 400 mg*	8	6.8	(1.8, 11.9)

Source: QT-IRT review, p. 2
*The largest lower bound is after Bonferroni adjustment for 3 time points.

Safety results
No death or SAE occurred in the study. Fifty seven patients were withdrawn for the study prematurely: 6/45 patients who received placebo, 6/45 patients who received placebo with moxifloxacin, 16/45 patients who received mifepristone 600 mg and 29/60 patients who received mifepristone 1800 mg. Fifty four of 57 patients were withdrawn because of AEs. The majority of patients who were withdrawn from the study due to the AEs received mifepristone. Overall, the most frequent AE that led to the study withdrawal was rash that developed in 49 subjects; 42/49 received mifepristone (27 subjects received 800 mg and 15 subjects received 600 mg). Other AEs that led to the study withdrawal were stomach ache, nausea, dizziness and vomiting, folliculitis, sore throat and pain, and occurred in 1 subject each. Overall, the most frequent AE that led to the study withdrawal was rash that developed in 49 subjects; 42/49 received mifepristone (27 subjects received 800 mg and 15 subjects received 600 mg). The event of rash that occurred in Study 300 is discussed in Section 7.3.5.

Other TEAEs
Overall, 120/195 patients (61.5%) experienced a total of 325 AEs. All AEs were mild to moderate in intensity. The highest proportion of subjects who experienced AEs received 1800 mg of mifepristone (48/ 60 (80.0%) subjects) followed by group of subjects who received 600 mg of mifepristone (28/ 45 (62.2%) subjects). Fewer patients who received placebo or placebo with moxifloxacin developed AEs, as expected: 21/ 45 (46.7%) subjects and 23/ 45 (51%) subjects, respectively. Headache was the most frequently reported adverse event in all treatment groups other than 1800 mg group. Headache occurred more frequently in patients who received Korlym (15/ 45 (33.33%) subjects in 600 mg group and 16/ 60 (26.7%) subjects

in 1800 mg group). In placebo and placebo plus moxifloxacin groups the headache was reported by 6/ 45 (13.33%) subjects, each. In group of patients who received 1800 mg of Korlym rash was the most frequent AE (28/60 (46.7%) subjects); 14/45 (31%) subjects who received 600 mg of mifepristone reported rash. No summary of TEAEs by treatment groups (mifepristone vs. placebo) and by mifepristone dose (1800 mg vs.600 mg) is provided by the Sponsor. The Sponsor stated that no clinically meaningful changes in vital signs, physical examination or clinical laboratory values occurred in any of the treatment group subjects. As per Sponsor, a transient, dose-dependent increase in ALT and AST levels occurred at the discharge visit and resolved at the safety follow-up visit (refer to Section 7.3.5). No cases of adrenal insufficiency were reported.

7.4.5.2 Study C1073-301 (Study 301): Rechallenge study for subjects who experienced a drug rash in Study 300.

Because of the unexpectedly high number of patients who was administered mifepristone and developed rash in Study 300, the Sponsor conducted additional safety Study C-1073- 301 to further investigate the mechanism of drug rash associated with mifepristone treatment

Study Objective
To evaluate the effect of rechallenge with mifepristone in 5 subjects who experienced a drug-related rash in Study 300, Part 1.

Study design
This was a Phase IIA rechallenge study of 11 days duration for subjects who experienced a drug rash in Study C-1073-300 Part 1. In this study all subjects received one dose each of 150 mg, 300 mg, 600 mg and 1200 mg, and seven doses of 1800 mg of mifepristone. Vital signs were measured and subjects underwent a full body visual inspection at the screening visit, Days 1 through 11, Day 14, Day 21, and Day 39.

Results
The five male subjects who experienced a drug-related rash after administration of mifepristone 1800 mg in the Part I of Study 300 were enrolled in the study. All five subjects completed the study, and none experienced a drug rash that was confirmed by a dermatologist. One subject reported an AE of 'rash' which was observed by staff, but not by dermatologist. A second subject reported an AE of 'rash', however, the study staff did not confirm any rash.

7.4.5.2 Study C1073-425 (Study 425): Placebo-controlled Study to Determine Effects of Mifepristone on High-density Lipoprotein Levels in Healthy Volunteers

Because the reduction in HDL levels was observed in patients with Cushing's syndrome in Study 400, the Sponsor designed the special safety study to evaluate further the effect of mifepristone on HDL levels.

Study objectives
To evaluate the effect of mifepristone on HDL levels as determined by several complementary techniques and to examine HDL particle functionality in healthy postmenopausal female volunteers taking 600 mg of mifepristone per day.

Design
The study was a Phase I, 14-week duration, randomized, double-blind, placebo-controlled study in 30 healthy female volunteers evaluating the effects of mifepristone on HDL-Cholesterol levels and HDL particle functionality in healthy volunteers. All subjects were randomized to receive mifepristone 600 mg (two 300-mg tablets) or matching placebo daily for 6 weeks and were followed for additional 6 week after the last dose of the study drug. Clinical laboratory tests included standard lipids evaluation (total cholesterol, HDL-C, LDL-C, and triglycerides), and lipids evaluation by beta quantification / ultracentrifugation (total cholesterol, LDL-C, VLDL-C and triglycerides), lipoprotein particle subclasses (VLDL, IDL, LDL, and HDL particles), apolipoproteins (AI, AII, B), fasting insulin and plasma glucose, cholesterol efflux assay. Lipids levels, apolipoprotein levels, HDL functionality, and relevant hormones levels were assessed at Days 1, 15, and Day 43 visits, standard lipid panel was evaluated at screening and on Days 1, 15, 43, and 84. Safety was evaluated by physical examination, vital signs, laboratory tests, and adverse events assessment. Transvaginal ultrasound and complete eye examinations were also incorporated in the study as per FDA advise (February 18, 2010); refer to Section 7.3.5 for the further discussion of the ophthalmologic and endometrial findings.

Treatment Groups:
All subjects were randomized to the two treatment groups (in 2: 1 ratio) to receive mifepristone or matching placebo once a day.

Criteria for evaluation of the effects of mifepristone on HDL
The changes from baseline to Week 6 for the following parameters were evaluated:
- lipid fractions including total cholesterol, HDL, LDL, and triglycerides by ultracentrifugation (beta quantification) and standard lipid assay
- lipoprotein subclass analysis by ion mobility
- apolipoproteins AI, AII, and B
- cholesterol efflux from macrophages
- HDL speciation measured by electrophoresis gels
- esterification/transfer studies (lecithin-cholesterol acetyltransferase (LCAT) and cholesterol ester transfer protein (CETP) activity
- testosterone, sex hormone binding globulin (SHBG), estradiol, estrone, LH, FSH
- fasting insulin and plasma glucose.

Statistical analysis

Effect of mifepristone on HDL- change in HDL level from baseline on Day 43- was evaluated by both assay (standard and beta quantitative) and was compared between the two treatment groups. Wilcoxon rank-sum test or t-test was used for the comparisons. Mean (±SD) of HDL levels and change-from-baseline results over time for each treatment group and obtained by each assay (standard and beta quantitative) were calculated on Day 1, Day 15, Day 43 and on Day 84 (for the standard assay only).The change from baseline in HDL on Day 43 evaluated with the standard and beta quantitation assays were compared by treatment groups separately. Linear regression was performed on this analysis and parameter estimates and corresponding 95% CI were calculated. Descriptive statistics were used to summarize the findings for all other safety evaluations.

Patient population and disposition
Healthy postmenopausal female volunteers, 45 - 65 years old, with normal liver and thyroid function tests, with baseline serum HDL level >40 mg/dL and triglyceride level <200 mg/dL, and not on lipid-reducing drugs or other drugs that interfere with lipid metabolism were eligible to participate in the study. Thirty postmenopausal women were enrolled in the study and received mifepristone (20 subjects) or placebo (10 subjects); 24 subjects completed the study. As per Sponsor, postmenopausal women were selected to obtain hormonally homogenous population. Six subjects in mifepristone group discontinued study prematurely: five subjects developed AEs (4 subjects developed rash and 1 subject developed abdominal pain, edema, body ache and fatigue) and one subject withdrew informed consent.

Results
Mifepristone produced a significant decrease in HDL levels compared to placebo, but had little effect on LDL, triglycerides, VLDL-C and ApoB. The major HDL protein component, ApoA-I also decreased. The concentration of ApoA-II did not change; this HDL protein component is more enriched in smaller HDL particles. The reduction in HDL was mostly due to a reduction in large, cholesterol enriched HDL_{2b} fraction. Efflux capacity of serum HDL declined with mifepristone treatment; the HDL function was preserved as demonstrated by normal lecithin-cholesterol acyltransferase (LCAT) and cholesteryl ester transfer protein (CETP) activity. The decline in cholesterol efflux was less than the decline in HDL. The Sponsor concluded that these observations indicate relative preservation of HDL's ability to facilitate reverse cholesterol transport from macrophages despite significant decreases in levels of HDL. Additionally, there were no changes in fasting glucose, insulin, or sex steroid hormones.

Safety Results
No death or SAE occurred during the study. Five subjects discontinued study early because of TEAEs; four subjects developed rash and one subject experienced abdominal pain, fluid retention, body aches, and fatigue. All of the events resolved with treatment.

Medical Officer's comments
Such symptoms as abdominal pain, fluid retention, body aches, and fatigue are suggestive of adrenal insufficiency that may occur during mifepristone treatment because of glucocorticoid receptor blockade. No other information including the duration of the event,

time of the occurrence of the event and treatment was provided by the Sponsor in this case, thus, not allowing an assessment of the causal relationship with mifepristone.

Non-serious TEAEs

Overall, 26/30 subjects (86.7%) experienced a TEAE: 18/20 subjects (90%) in mifepristone group and 8/10 subjects (80%) in the placebo group. Treatment-emergent AEs that occurred in two or more subjects in the mifepristone group included peripheral edema (6 subjects), nausea and fatigue (4 subjects each), and blood testosterone increased and weight increased (3 subjects each). No changes in laboratory values, physical examination findings, vital signs, ECG, eye findings, or transvaginal ultrasound findings were reported. One subject developed a small fluid collection in the uterine cavity that was stable at the end of the study and did not require endometrial biopsy.

7.4.6 Immunogenicity

Not applicable. Korlym is not a therapeutic protein.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The Sponsor investigated the frequency of TEAEs per each dose level in Study 400. The dose dependency analysis is discussed in Section 7.2.2. Overall, the conclusion regarding the relationship between dose and frequency of TEAEs including SAEs could not be drawn: the doses and duration of the treatment with each dose varied extensively in each patient, the doses could have been increased or decreased during the study, and only few patients were on stable dose during the study. Moreover the overall patient population enrolled in the study was small, the number of patients per each dose level group was unbalanced and number of AEs by system organ class (SOC) and preferred term (PT) was too small, complicating the interpretation of the findings even more. No dose dependency analysis was performed in Study 415; this study included only abbreviated report.

7.5.2 Time Dependency for Adverse Events

Time of the occurrence of the AEs was evaluated in 30 patients who participated in both trials by comparing type and frequency of AEs reported during the long-term extension Study 415 with those reported during Study 400 (Table 64). The profile of reported TEAEs during long-term treatment with Korlym appeared to be similar to the profile of AEs reported in Korlym studies of the shorter duration (Study 400): fatigue, headache and nausea were the most commonly reported TEAEs reported in Study 400 and in Study 415, although the incidence of fatigue and nausea was lower in Study 415 as compared to Study 400. The Sponsor hypothesized that these subjectively reported AEs usually occur more commonly when patients start a new drug and diminish over time or patient becomes "used" to them and no longer mentions them. Such objective TEAEs as hypokalemia and endometrial thickness occurred at similar rates in both studies. Higher incidence of hypercholesterolemia and of increased

testosterone levels occurred in the extension study compared to the incidence of these events in Study 400. The higher incidence of increased testosterone levels in Study 415 may be due to the normalization of LH levels (Nieman et al, 1985) (the LH and FSH levels were not monitored in the studies). Patients with Cushing's syndrome have inhibition of gonadotropin release from the pituitary gland by high cortisol levels, thus, LH secretion may increase due to the blocking of the glucocorticoid receptors by Korlym at the pituitary level (Lindsay et al, 2005).

All other common TEAEs (in > 10% of subjects) were observed less frequently in Study 415 than in Study 400. The change in frequency of observed TEAEs may be due to the overall small number of patients, less dosage variability in Study 415 and/or improved drug tolerance with longer treatment duration. Overall, the number of patients enrolled in both studies and number of reported AEs by SOC and PT was small, the frequency of the AEs evaluation during the studies was different (every 2- 4 weeks during the Study 400 and every 6 months during the Study 415) complicating the interpretation of the findings even more.

Table 64. Comparison of Treatment-emergent Adverse Events (Occurring in Three or More Subjects) Starting in Study 400 and Study 415 by System Organ Class and Preferred Term (Safety Population)

System Organ Class **Preferred Term**	**TEAE Starting in Study 400** **N=30 n (%)**	**TEAE Starting in Study 415** **N=30 n (%)**
Subjects with at least 1 TEAE	28 (93.3)	30 (100.0)
Endocrine disorders		
Cushing's syndrome	3 (10.0)	2 (6.7)
Gastrointestinal disorders		
Abdominal pain	3 (10.0)	1 (3.3)
Constipation	3(10.0)	1 (3.3)
Diarrhea	6 (20.0)	2 (6.7)
Dry mouth	6 (20.0)	0
Gastroesophageal reflux disease	4 (13.3)	1 (3.3)
Nausea	16 (53.3)	8 (26.7)
Vomiting	9 (30.0)	4 (13.3)
General disorders and administration site conditions		
Fatigue	15 (50.0)	8 (26.7)
Edema	3 (10.0)	0
Edema peripheral	7 (23.3)	5 (16.7)
Pain	4 (13.3)	1 (3.3)
Thirst	3 (10.0)	0
Infections and infestations		
Nasopharyngitis	5 (16.7)	5 (16.7)
Sinusitis	5 (16.7)	2 (6.7)
Urinary tract infection	3 (10.0)	2 (6.7)
Investigations		
Blood cholesterol increased	1 (3.3)	3 (10.0)
Blood potassium decreased	9 (30.0)	9 (30.0)
Blood testosterone free increased	0(0.0)	3 (10.0)
Blood testosterone increased	1 (3.3)	3 (10.0)
Blood triglycerides increased	4 (13.3)	0

Thyroid function test abnormal	8 (26.7)	5 (16.7)
Metabolism and nutrition disorders		
Anorexia	3 (10.0)	0
Decreased appetite	9 (30.0)	2 (6.7)
Musculoskeletal and connective tissue disorders		
Arthralgia	8 (26.7)	2 (6.7)
Back pain	5 (16.7)	3 (10.0)
Myalgia	6 (20.0)	1 (3.3)
Pain in extremity	3 (10.0)	1 (3.3)
Nervous system disorders		
Dizziness	8 (26.7)	5 (16.7)
Headache	16 (53.3)	7 (23.3)
Somnolence	4 (13.3) .	1 (3.3)
Psychiatric disorders		
Anxiety	4 (13.3)	4 (13.3)
Renal and urinary disorders		
Pollakiuria	3 (10.0)	0
Reproductive system and breast disorders		
Endometrial hypertrophy	9 (30.0)	6 (20.0)
Metrorrhagia	3 (10.0)	2 (6.7)
Vaginal hemorrhage	3 (10.0)	3 (10.0)
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	3 (10.0)	2 (6.7)

Source: Sponsor's table 7, Module 5, CSR 415, 4-month update, pp 30-31.
TEAEs of special interest are highlighted.
TEAEs that occurred more frequently in Study 415 are in red font.

7.5.3 Drug-Demographic Interactions

Safety data for Korlym in Cushing's syndrome studies were not analyzed by age, sex, or race because of the small sample sizes. There are known reproductive side effects of mifepristone in women, including vaginal bleeding and endometrial thickening that are discussed in Section 7.3.5 and the propensity of mifepristone to terminate pregnancy that is discussed in Section 7.6.2.

7.5.4 Drug-Disease Interactions

The PK of mifepristone in patients with renal impairment and hepatic insufficiency is discussed in details in Dr. Jee Eun Lee's review and in Section 4.4.3.

Study C1073-19: Renal Insufficiency
The PK of mifepristone was evaluated in subjects with severe renal impairment but who are not on dialysis (glomerular filtration rate ((GFR) <30 mL/min/1.73 m2). The results of the study demonstrated that mean exposure to mifepristone increased by 31 %, with similar or smaller increase in metabolite exposure. The Sponsor concluded that no change in the initial

dose of (b) (4) is needed for severe renal impairment, but the maximum dose should not exceed 600 mg per day.

Study C1073-05: Hepatic Insufficiency
This study was conducted in subjects with moderate hepatic impairment only (Child-Pugh Class B) to evaluate the pharmacokinetics of mifepristone. The PK results were similar in hepatically-impaired and healthy subjects. The Sponsor concluded that no dosage adjustment is necessary in patients with mild to moderate hepatic impairment. Clin.Pharm reviewer agreed with the Sponsor's recommendations however recommended that the maximum dose should not exceed 600 mg per day in patients with moderate hepatic impairment, and Korlym should not be used in patients with severe hepatic impairment.

7.5.5 Drug-Drug Interactions

The drug-drug interactions studies submitted by the Sponsor are discussed in details by Dr. Jee Eun Lee; please refer to the Clin. Pharm review for the details.

Briefly, in vitro studies indicated there was a potential for mifepristone and/or its metabolites to inhibit oxidative drug metabolism mediated via CYP2A6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4, and to inhibit transport via P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Thus, three clinical studies in healthy subjects have been conducted to evaluate an interaction between multiple dose of mifepristone and the CYP3A4 substrates simavastatin and alprazolam, the CYP3A inhibitor cimetidine, the CYP2C8/2C9 substrate fluvastatin, and the P-gp substrate digoxin. The Sponsor choice to evaluate CYP3A4 and CYP2C8/2C9 was based on the fact that CYP3A4 is responsible for the metabolism of the largest proportion (over 50%) of drugs on the market, and CYP2C8/2C9 are the next most common isoenzymes involved in drug metabolism (Study C1073-l6). A drug-drug interaction study with a prototypical mild/moderate CYP3A inhibitor, cimetidine (Study C-1073-26) was conducted because mifepristone may initially inhibit and later induce its own metabolism.

Drugs Metabolized by CYP3A4 (studies C1073-24 and C1073-25)
Concurrent use of mifepristone with a drug whose metabolism is mediated by CYP3A4 may increase plasma concentrations of this drug. The drug-drug interaction studies demonstrated, that mifepristone increased exposure to alprazolam by 70% and exposure to simvastatin by more than 10-fold in healthy subjects. Clin. Pharm reviewer noted that the dose of simvastatin concomitantly administered with mifepristone on Day17 was 80 mg, and on Day 1 and 7-40 mg. The Sponsor concluded and Clin. Pharm reviewer agreed with conclusion that the discontinuation or dose reduction of such medications, including triazolam, felodipine, cyclosporine, everolimus or sildenafil with mifepristone co-administration. Additionally, concomitant use of simvastatin or lovastatin should be contraindicated because of the increased risk of myopathy and rhabdomyolysis.

CYP3A Inhibitors (Study C1073-26)
Medications that inhibit CYP3A could increase plasma mifepristone concentrations and dose reduction of mifepristone may be required. Co-administration of mifepristone with mild CYP3A inhibitor cimetidine (800 mg/day) was evaluated in healthy subjects and showed no evidence of a changed exposure to mifepristone. Thus, mild to moderate inhibitors of CYP3A require no dose adjustment of mifepristone. Although no studies with strong CYP3A inhibitors were conducted up-to-date, the Sponsor stated that co-administration of strong CYP3A inhibitors including ketoconazole, itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, and fosamprenavir with mifepristone may increase exposure to Korlym, and, thus these drugs should not be used in combination with Korlym. Clin. Pharm reviewer disagreed with the Sponsor and recommends avoiding co-administration of moderate CYP3A inhibitors with Korlym. The Clin. Pharm reviewer also recommends investigating further DDI between moderate/strong CYP3A inhibitors and Korlym.

CYP3A Inducers
No medications that induce CYP3A have been studied when co-administered with Korlym. However, the Sponsor recommends avoiding co-administration of Kolrym and CYP3A inducers such as rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, and St. John's Wort.

Drugs Metabolized by CYP2C8/2C9 (Study C1073-16)
Co-administration of Korlym with drugs whose metabolism is mediated by CYP2C8/2C9 increases plasma concentrations of these drugs. Co-administration of mifepristone with fluvastatin increases increased exposure to fluvastatin in healthy subjects by 2.7-fold. Thus, the Sponsor recommended that the drugs metabolized by CYP2C8/2C9 including non-steroidal anti-inflammatory drugs, warfarin, and repaglinide should be used at the smallest recommended doses and closely monitored for adverse effects when given concomitantly with mifepristone.

Drugs transported by P-gp (Study C1073-23)
Mifepristone increased exposure to digoxin by 40% and decreased mean renal digoxin clearance by 12% as demonstrated in healthy subjects. Thus, the Sponsor recommended that the plasma digoxin concentration should be measured after 1 to 2 weeks of concomitant use and at appropriate intervals thereafter. The Sponsor also concluded that the extent of the demonstrated interaction will have only minor effects for other drugs with P-gp mediated drug transport.

Drugs transported by BCRP
No clinical studies have been performed to evaluate the inhibitory effects of mifepristone on BCRP. However, the Sponsor recommended using smallest doses of the drugs in which BCRP has a major role in disposition when such drugs are given concomitantly with mifepristone.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Two-year carcinogenicity studies conducted in rats and mice demonstrated an increase in thyroid and liver neoplasms in rats only (refer to Dr. Patricia Brundage's review). As per Sponsor, the liver and thyroid neoplasms are common tumors in the rat, and occur with drugs, such as mifepristone, that cause microsomal enzyme induction in rats. The mouse study showed no increase in any tumors associated with a lifetime of dosing with mifepristone. All PTs under the SOC Neoplasms Benign, Malignant and Unspecified for the studies in Cushing's syndrome (400 and 415) were reviewed; no data was submitted from the other supportive studies (abbreviated reports were available only). Overall, no individual neoplasm PT appeared more than once in Korlym-treated subjects with Cushing's syndrome. Longer treatment duration with Korlym might be required to reliably assess the long-term risk of carcinogenicity.

7.6.2 Human Reproduction and Pregnancy Data

Mifepristone is a potent progesterone antagonist and was approved in the United States since 2000 as Mifeprex for the early termination of pregnancy. The approved dosing is 600 mg (three 200 mg tablets).
Overall, the risk of termination of pregnancy in patients with Cushing's syndrome is low since this patient population is unlikely to become pregnant. The exact mechanism of decreased fertility in these patients is unknown; amenorrhea is a common feature of hypercortisolemia and observed in 35-86% of females with Cushing's syndrome (Nieman, 2010). The proposed etiology of amenorrhea and infertility is a hyperandrogenism and hypercortisolemic inhibition of gonadotropin release from the pituitary gland. Pregnancies that occur in patients with untreated Cushing's syndrome are associated with significant maternal and fetal morbidity and mortality including increased rates of spontaneous abortion, perinatal death, premature birth, and intrauterine growth retardation. Approximatley 136 pregnancies in 122 patients with Cushing's syndrome (seven patients had more than one pregnancy), resulting in 107 live births were described in world literature (Lindsay et al, 2005). Forty-three percent of the births were premature; there were 8 stillbirths, 6 intrauterine deaths/spontaneous abortions, one ectopic pregnancy, 6 therapeutic abortions, and 3 cases with an uncertain outcome. The treatment of hypercortisolemia reduces but does not abolish these adverse outcomes.

Because of the concern of whether specific precautions are necessary for the use of this medication in the intended female population of reproductive age, the Maternal Health Team and the Division of Reproductive and Urologic Products (DRUP) were consulted; please refer to these consult in DARRTS for the details.

- The Maternal Health Team concluded the following:

"Although the maternal and fetal implications of Cushing's disease in pregnancy are significant, the small number of patients treated at the NIH over fifteen years and the relatively small number of reports in the literature indicate that the menstrual irregularities resulting

from Cushing's syndrome decrease the pregnancy rate in this population. However, because the diagnosis of Cushing's syndrome is challenging and a range of menstrual irregularities are seen among affected females, pregnancy may occur in a small subset of patients with Cushing's syndrome who are of childbearing age. This possibility should be noted in labeling". The Maternal Health Team also noted that mifepristone inhibits ovulation by *"disruption of the follicular maturation and inhibition of the LH surge (Shoupe et al, 1987)."*

- The DRUP noted the following in response to questions from DMEP:

Question1. Is pregnancy possible in females with Cushing's disease on the proposed Korlym doses?
DRUP indicated that the *"pregnancy is likely to occur at a significantly reduced rate in women with Cushing's disease who are being treated with daily doses of Korlym of at least 300 mg. Studies have demonstrated that low daily doses of mifepristone can prevent ovulation in 13-20% of women or disrupt/delay normal endometrial maturation"*.
Question 2: Do the proposed doses of Korlym when taken chronically carry the risk of pregnancy loss in patients with Cushing's syndrome?
DRUP indicated that *"the proposed doses of Korlym when taking chronically carry the risk of pregnancy termination in patients with Cushing's syndrome, although the drug is less effective for pregnancy termination when compared to the combined regimen mifepristone/ prostaglandin.*
Question 3: Do additional precautions need to be given to the female patients of child-bearing age while taking Korlym?
DRUP indicated that "t*he probability of conception or pregnancy survival is extremely low. However, if an individual of reproductive age is adamantly opposed to abortion, it may be recommended that she use an acceptable non-hormonal method of contraception before and throughout the use of Korlym for the proposed indication".*

In the Korlym (mifepristone) clinical development program, no pregnancies occurred in patients receiving mifepristone (Korlym). However, in consideration of mifepristone's abortifacient effects, additional precautions were undertaken in female patients in the clinical trials, including a requirement for a pregnancy test prior to the first administration of the drug, and a repeat pregnancy test any time treatment with mifepristone was interrupted for more than 7 days. Additionally, all female patients participating in the clinical trials were required to use non-hormonal contraceptive measures, including abstinence, throughout the trials. In conclusion, even though the risk of pregnancy is very small in intended patients' population, the Sponsor recommends excluding pregnancy before the initiation of treatment with Korlym and for one month after stopping treatment by the use of a non-hormonal, medically acceptable method of contraception in patients of child-bearing potential. Additionally, nursing mothers should not be treated with Korlym, because it is not known whether or not Korlym is excreted in human milk.

7.6.3 Pediatrics and Assessment of Effects on Growth

Cushing's syndrome is extremely rare in pediatric population. The incidence of Cushing's syndrome in children is estimated at approximately 0.2 cases per 1 million persons per year.

Thus, Korlym for the treatment of Cushing's syndrome was granted orphan designation by the FDA on July 5, 2007 and was exempted from pediatric assessment under Pediatric Research Equity Act (PREA).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose
No incidences of overdose have been reported in Corcept-sponsored trials of mifepristone. The drug blocks glucocorticoid receptor, thus, an overdose during the chronic administration of Korlym may lead to the development of adrenal insufficiency and patients should to be monitored closely for signs of adrenal insufficiency. Glucocorticoid blockade with mifepristone is reversible with administration of a glucocorticoid.

Drug Abuse
No abuse potential is expected with Korlym.

Withdrawal and Rebound
It is expected that signs and symptoms of Cushing's, as well as associated laboratory values, will return to pretreatment levels after withdrawal of Korlym. The administration of Korlym was interrupted up to 6 weeks during the follow-up period in Study 400 until patients restarted treatment with Korlym in Study 415. The Sponsor indicated that symptoms of hypercortisolemia and laboratory values were not worse when compared to the symptoms and laboratory values at baseline visits before initiation treatment with Korlym in Study 400 (i.e. no rebound effect was observed).

7.7 Additional Submissions / Safety Issues

7.7.1 120-day safety update

The 120-day safety update provided additional information about the TEAEs and serious adverse events from the ongoing study of Korlym (Study 415), the reanalyzed ECG data of the outliers from studies 400 and C-1073-71 by the cardiologist, the MRI data from studies 400 and 415 analyzed at central reading facility and data obtained in three patients who received mifepristone on a compassionate use basis (one patient) and in Study 405 (two patients). Overall, no new safety signals were identified during the period covered by this 120-day safety update.

Study 415
The safety data for 20 patients who were enrolled in the study before 15 September 2010 (the cut-off data for Study 415 data in the original NDA) and for additional 10 patients who have entered the study between 15 September, 2010 and 27 May, 2011 are discussed in Section 7, in the respective subsections.

Pituitary MRI assessment from 35 patients enrolled in studies 400 and 415

A retrospective analysis of pituitary MRI information obtained in patients with Cushing's disease participating in studies 400 and 415 was conducted (MRI images were centrally analyzed). The original MRI findings are discussed in Section 7.3.5. Forty three patients with Cushing's disease were enrolled in these studies; 41/47 patients underwent MRI of pituitary. Of these 41 patients, 37 patients had at least one post-baseline MRI. Images of 35/37 patients were available for the analysis; the Sponsor did not provide further information about the two cases that were excluded from the analysis. The median time of treatment with Korlym was 5.7 months (range: 0.9-27.1 months). Twenty-eight patients had images available for the 24 weeks of treatment on Study 400; 14 patients had images available through the Month 6 visit on Study 415; and 13 patients had images available after at least one year of treatment.
Sixteen of 35 analyzed patients had a visible pituitary tumor at baseline. Four subjects had possible increase in tumor size. Overall, the increase in tumor size was small or inconclusive in all cases and did not raise any new safety concerns with Korlym use at present time. Briefly:

- Patient # 08-004 had increase in an invasive adenoma from baseline (Study 400) to Month 25 visit (Study 415): from 13 x 15 mm to 15.5 x 18.6 mm. Overall, the increase in each dimension was small.
- Patient #22-003 had an increase in size of a pituitary adenoma on Study 400 from baseline (27 x 46 mm) to Week 10 (32 mm x 52 mm), and this patient was diagnosed with pituitary cancer with liver metastasis. Thus, the tumor growth may reflect the progression of cancer and not effect of study drug itself. Of note, this patient's MRI obtained 4 months prior to the study entry demonstrated the progression of the tumor size at study entry as compared to the initial image.
- Patient # 03-004 had tumor progression in one dimension only (from 10.8 mm x 9.5 mm to 10.8 mm x 11.8 mm) at Week 24 in Study 400, which was not reported originally by Investigator. The overall increase is small, and in only one dimension, thus the increase may be due to the reading error.
- Patient # 10-003 was found to have initial regression of the pituitary tumor from baseline (8.3 mm x 8.8 mm) to Week 10 (7.5 mm x 6.5 mm) followed by progression at Week 24 (9 mm x 9 mm). The difference in the size of tumor at last visit as compared to baseline is small and might be due to the reading error (change 0.7 mm x 0.2 mm).

Additionally, the increase in tumor size in patient # 08-005 (refer to Section 7.3.5) reported in the original NDA submission was not confirmed by the retrospective analysis.

Update on ECG Findings: Cardiologist's Assessment of ECG Interval Data in Patients with QTcF Outlier Values in Study 71 and Study 400
ECG data from patients with outlier values of QTcF > 450 ms or change-from-baseline QTcF (Δ QTcF) exceeding 30 ms were re-evaluated by a cardiologist; the original evaluation was a machine-read ECG. No new data was identified that would change risk/benefit assessment of the drug. The original ECG findings are described in Section 7.3.5.

Briefly, in Study 400, 4/5 originally identified patients with QTcF > 450 ms or Δ QTcF > 30 ms still had abnormal QTcF or Δ QTcF values comparable with machine's readings; one patient (#07- 009) did not have any outliers values after correction. As a result of cardiologist's

re-evaluation there was only one patient (# 11-004) whose QTcF was longer than the machine-read value (406 ms vs. 396). This patient was originally reported as having abnormal Δ QTcF of 51.7 ms; the Δ QTcF remained abnormal after correction (+39 msec). The prolongation of QTcF interval at both visits in patient 08-003 was attributed to the presence of bundle branch block (bifascicular) with QRS 154 msec. Patient 01-001 also had left bundle branch block with prolonged QRS at baseline (126 msec) and on Day 14 (128 msec).

In Study C1073-71, 5/9 patients initially identified as having abnormal QTcF interval or Δ QTcF > 30 ms still had abnormal values after cardiologist-correction of ECG intervals; four patients initially reported as having prolonged QTcF interval or ΔQTcF were considered to have no ECG abnormalities after correction. Four of five patients with abnormal values had either a longer (3 patients) or the same (1 patients) QTcF interval at screening as originally identified by machine. One patient on placebo, 09-060, had a longer but still normal ΔQTcF of 29 msec (from a baseline value of 434 msec to 463 msec at the Day 14 visit). None of the patients exhibited a ΔQTcF > 30 msec. Overall, no new conclusions could be drawn, and no new safety concern with Korlym was raised after the repeated ECG analysis.

Safety Update from Compassionate Use of mifepristone in three patients with Cushing's syndrome

Three patients received mifepristone for the treatment of Cushing's signs and symptoms under compassionate use: two patients were enrolled in Study C1073-405 (Study 405 hereafter) and one patient with pituitary ACTH-producing tumor received treatment with mifepristone (b) (4) Study 405 was designed for treatment of Cushing's patients who were not eligible for the primary safety and efficacy study. Two patients, one with adrenal carcinoma and one with ectopic ACTH-secreting tumor were enrolled in this study.

Death

None of patients died

SAE

Two SAE occurred in one patient in Study 405 (#19-101): one SAE was considered not drug related. The Sponsor did not indicate the relationship of the second event with the study medication. These SAE were:

1. Hematuria, the event was classified as not-related to the study drug
2. Altered mental status.

The event was associated with hypoglycemia, hyperkaliemia, and hypotension. The treatment with mifepristone was temporary interrupted for 1 week. No other information, such as concomitant treatment with glucocorticoids was provided by the Sponsor.

Medical Officer's comments

In this reviewer opinion, such symptoms as hypoglycemia, hyperkaliemia and hypotension are typical features of the adrenal insufficiency, thus the occurrence of adrenal insufficiency can not be ruled out and the event should be considered drug related.

Narratives for three patients who received mifepristone for the treatment of Cushing's signs and symptoms under compassionate use:

- Patient #19-101, a 44 year old male with Cushing's syndrome due to metastatic adrenal carcinoma received treatment with mifepristone in Study 405. His medical history was significant for hypertension and hyperlipidemia. Prior to the study enrollment, patient received chemotherapy including mitotane 3000 mg BID. The initial dose of mifepristone was 300 mg once daily (started on Dec 2, 2010); the dose was increased to 600 mg once daily in 14 days. Two SAE occurred in this patient during treatment with mifepristone: hematuria (b) (6)); this event was considered not-drug related and altered mental status. The second SAE (altered mental status, hypoglycemia, hyperkaliemia, and hypotension) developed in 1 month after the initiation of the treatment of mifepristone; the dose of mifepristone was 600 mg once daily at the time of the event. The treatment with mifepristone was temporary interrupted for 1 week due to the development of this SAE; the treatment was restarted at 300 mg once daily. The dose was subsequently increased to 600 mg once daily in 14 days, and later to 900 mg. Overall patient was treated with mifepristone for 6 months; the mifepristone was discontinued on 31 May 2011 because of progression of the adrenal carcinoma. Patient was treated with an investigational IGF-l receptor inhibitor (b) (4) for 2 weeks, but developed confusion. Thus, the investigational drug was discontinued and mifepristone was restarted again on June 13,011; the patient's mental status improved. No other efficacy results provided in this patient by the Sponsor.
- Patient #19-102 is a 68 year old man with Cushing's syndrome due to an ectopic ACTH-secreting mediastinal carcinoma was enrolled in Study 405 and initiated treatment with mifepristone on March 15, 2011. His medical history is significant for DM, hypertension, hyperlipidemia, and COPD, lower extremity edema, altered mental status with weakness and myopathy. Patient was treated with ketoconazole in past, but dose was discontinued within few days (the Sponsor did not provide the reason for the ketoconazole discontinuation). The initial dose of mifepristone was 300 mg once daily; the dose was increased to 600 mg in 14 days. As per Investigator, diabetes, hypertension and weakness improved as a result of treatment. Patient was treated with mifepristone for total of 23 days; the drug was discontinued and patient underwent successful resection of the neuroendocrine carcinoid.
- A 47 year old female with Cushing disease was treated with mifepristone under Investigator-sponsored IND. Patient presented with worsening of DM (HbAlC 13.3%), fatigue, weakness, hallucinations, volume overload, and osteopenia and was diagnosed with Cushing's disease due to a pituitary macroadenoma. She underwent incomplete resection of the pituitary tumor, was treated with cabergoline and ketoconazole postoperatively. Due to the persistent hypercortisolemia in spite of treatment, 600 mg of mifepristone was added to her treatment regimen in preparation for adrenalectomy. As reported by the Sponsor, her requirements for insulin and anti-hypertensive medications decreased and mental status improved. After 2 weeks of treatment with mifepristone patient developed an adverse event (the Sponsor did not report whether the event was considered SAE) that included symptoms characteristic of adrenal insufficiency: hypotension, hypoglycemia, anorexia. Mifepristone was discontinued and dexamethasone was administered; ketoconazole and cabergoline were continued. Mifepristone levels were measured after discontinuation of mifepristone and were found to

be greatly elevated. In August 2009, the patient underwent successful bilateral adrenalectomy.

Medical Officer's comment:
Patient was treated with ketoconazole and mifepristone concomitantly. Ketoconazole inhibits CYP3A isoenzyme and increase plasma mifepristone concentrations (the Sponsor indicated that mifepristone levels were found to be greatly elevated in this patient. Thus, in this reviewer opinion, the adrenal insufficiency in this patient occurred because of the concomitant use of ketoconazole and mifepristone. The Sponsor already recommended in the Korlym label to avoid co-administration of ketoconazole and mifepristone (refer to Section 7.5.5).

Safety Update from Study in Normal Subjects
Study C-108297-102 is a single-center, double-blind, placebo-controlled study in healthy volunteers evaluating the safety, tolerability, and PK of a multiple dose regimen of mifepristone for the prevention of weight gain associated with use of antipsychotics. Subjects in Cohort 3 of the study were randomly assigned to receive 600 mg of mifepristone daily or placebo for up to 14 days instead of CORT-108297. The subjects in Cohort 3 also received a single daily dose of prednisone 20 mg on Days 7, 1, 7, and 14 to determine the effects of 600 mg mifepristone on suppressing of the acute corticosteroid effects.

Safety results
No deaths or SAE occurred in the study.
AE that led to study discontinuation: two subjects in cohort 3 who received mifepristone developed rash and were withdrawn from the study.
Other TEAEs: Eight of 10 (80%) subjects who received mifepristone and 3/ 4 (75%) subjects who received placebo experienced at least one AE during the study. Drug-related AEs were reported more frequently in mifepristone subgroup (19 events in 6/10 subjects) than in placebo subgroup (2 events in 1 subjects). Most of the drug-related adverse events were gastrointestinal AEs including dry mouth, abdominal pain, flatulence, constipation, dyspepsia, nausea and nervous system AEs including headache, dizziness, hot flush, and asthenia. Headache was the most frequent complaint in the mifepristone subgroup (6/10 subjects); none of patients who received placebo complained of headache. No clinically significant changes in the laboratory parameters or vital signs were reported.

7.7.2 Literature review

None of the published reports of the use of mifepristone in patients with Cushing's syndrome included formal safety evaluations.

Exposure (Table 65)

In published studies mifepristone doses ranged from 200 to 2000 mg/day or approximately 5 to 30 mg/kg/day. The duration of treatment ranged from 1 week to 24 months. Mifepristone

doses were frequently adjusted during treatment to increase efficacy or in response to the adverse events.

Table 65. Mifepristone Doses Used in the Treatment of Patients with Cushing's syndrome

Type of Cushing's syndrome (Reference)	N of pts	Dose	Duration
Cushing's Disease (Chu et al, 2001; Castinetti et al, 2009)	5	400 to 2000 mg/day	0.5 to 24 months
Ectopic ACTH (Chrousos et al, 1989; Bilgin eat al, 2007; Cassier et al, 2008; Castinetti et al, 2009)	14	400 to 1600 mg/day 5 to 22 mg/kg/day	10 days to 18 months
ACTH-dependent Cushing's of unknown origin (Beaufrere et al, 1987)	1	5 to 20 mg/kg/day	2 months
Adrenal carcinoma (Contreras et al, 1987; Chrousos et al, 1989; Donckier et al, 1989; van der lely et al, 1991; Castinetti et al, 2009)	17	200 to 2000 mg/day 5 to 30 mg/kg/day	0.25 to 21 months
Benign adrenal tumor (Chrousos et al, 1989)	1	5 to 22 mg/kg/day	6 weeks
Adrenal hyperplasia (Castinetti et al, 2009)	1	600 mg/day	6 months
Unspecified Cushing's Syndrome (Chrousos et al, 1989, Newfield et al, 2001)	5	400 mg/day 5 to 22 mg/kg/day	3 days to 12 months

Source: Sponsor's table 2, Module 5, Vol 39, module 5, Literature review, p. 7.

Adverse events were reported in 35/51 patients (Table 66). The most serious adverse event associated with mifepristone, adrenal insufficiency (with hypotension), was reported in ten patients. Three patients developed hypotension, seven patients had nausea, vomiting, or lethargy, but without hypotension. All of these patients were treated successfully with dexametahsone. One patient discontinued mifepristone therapy due to adrenal insufficiency. The most commonly reported adverse effect was hypokalemia (14 patients). Treatment of hypokalemia required use of the large doses of potassium, and spironolactone. Two patients discontinued mifepristone due to persistent hypokalemia. Other reported adverse effects included hypertension (5 patients), pneumonia (3 patients), gynecomastia and hypoglycemia (2 patients each), impotence, water retention, vaginal bleeding and eosinophilia (1 patient each). Mifepristone was discontinued in eight patients due to the AEs, including endometrial hyperplasia (1 case), hypokalemia (2 cases), nausea and prostration (1 case), nausea (1 case), Pneumocystis pneumonia (1 case), and hypotension due to the adrenal insufficiency (2 cases). Five patients were continued treatment with mifepristone at the time of reporting. No adverse effects were reported in 16 patients.

Medical Officer's comment:
1. There was one episode of eosinophila with hypoglycemia reported in one patient. Hypoglycemia and eosinophila are frequent signs of the adrenal insufficiency; thus, the development of adrenal insufficiency in this patient can not be excluded.
2. Three cases of Pneumocystis jiroveci (P. carinii) (5, 11) were reported. Pneumocystis infection has also been reported after treatment of Cushing's syndrome with surgery or medications (ketoconazole, octreotide, metyrapone) (15-17). The occurrence of PCP

pneumonia might be due to the activation of latent infection with lowering the cortisol levels (or with elimination of glucocorticoid action by blocking the receptors) and not to the drug itself.

Table 66. Safety Observations during Mifepristone Treatment of Cushing's syndrome

	N	Age	Etiology (n)	Clinical/Biochemical Findings (n)	Dose
Beaufrere et al, 1987	2	27 mth		No side effects noted	25 mg three times a day (5 mg/kg)
Bilgin et al, 2007		46 y/ F		No adverse events reported Patient died of progression of metastatic lung cancer	
Cassier et al, 2008	2	46 y/ F	ECS *	Hypokaliemia, no other side effects reported	
		37 y/ F	ECS	Hypertension and continuing hypokalemia	
Castinetti et aI, 2009	20	N/S	CD (4)	Signs of adrenal insufficiency (1) High blood pressure and severe hypokalemia (1)	Median starting dose : 600 mg/day (300-600 mg) Median maximal dose: 700 mg/day (600-1200 mg)
		N/S	ECS(3)	Worsening hypokalemia (3) Worsening hypertension (2)	Median starting dose : 400 mg/day (400-600 mg) Median maximal dose: 600 mg/day (600-800 mg)
		N/S	Adrenal carcinoma (12)	Adrenal insufficiency (2) 7/12 patients developed hypokaliema, which resulted in discontinuation of mifepristone in 1 patient	Median starting dose : 400 mg/day (200-1000 mg) Median maximal dose: 600 mg/day (400-2000 mg)
		N/S	Adrenal hyperplasia (1)	Hypokaliemia unchanged	600 mg/day
Chrousos et al, 1989	11	N/S	ECS (7); unspecified (4)	4 patients withdrawn from mifepristone between 3 and 14 days of starting drug due to -hypotension (1), -severe nausea and prostration (1), -possible inhibition of cortisol biosynthesis (1) -Pneumocystis carinii pneumonia (1) 2 patients developed adrenal insufficiency Other AEs included gynecomastia (2), nausea (2), impotence (1), hypothyroidism (1), and adrenal crisis (1) No hematologic, dermatologic, renal, or liver toxicity	5-22 mg/kg/day

				observed	
Chu et al, 2001	1	51 y/ M	CD	Severe hypokaliema(<3 mEq/L) Episode of adrenal insufficiency at month 10 (mifepristone 800 mg/day); responded to dexamethasone and mifepristone dose reduction	400-1200 mg/day (6 mg/kg/day-25 mg/kg/day)
Contreras et al, 1987	1		Adrenal carcinoma	Hypoglycemia, water retention, polymenorrhea Clinical suggestion of adrenal insufficiency	20-30 mg/kg/day
Donckier et al, 1989	1	62 y/ M	Adrenal carcinoma	No AEs reported	400 mg/day
Newfield et al, 2001	1	13 y/ F	Unspecified	Mifepristone discontinued due to vaginal bleeding, endometrial hyperplasia and enlarged uterus.	400 mg/day
Nieman et al, 1985	1		EAS	No AEs reported	5-20 mg/kg/day
Nieman et al, 1987	1	30 y/ M	EAS	No AEs reported	
Oosterhuis et al, 2007	2	62 y /F 57 y/F	EAS	2 life-threatening cases of Pneumocystis jiroveci pneumonia	
Van der Lely, 1991	2	43 y /M	Adrenal cancer	Hypoglycemic episodes with eosinophila -resolved with lower dose of mifepristone (1) Patient died due to tumor progression (1)	400-800 mg/day
		32 y/F	Adrenal cancer	No AEs reported	

Source: Sponsor's table, Module 5, Vol 39, Literature review, p.12.
Cases of adrenal insufficiency are in red font.

8 Postmarket Experience

Korlym is not currently marketed for the treatment of Cushing's syndrome. Therefore, post-marketing data are not available.

Mifepristone was approved as Mifeprex for the pregnancy termination in dose 600 mg in September 2000 and is marketed in US since than. Two cases of serious bacterial infection, one report of a myocardial infarction and "a small number of reports of ruptured ectopic pregnancies" were submitted by Danco Laboratories since drug approval. No causal relationship between any of these events and the use of mifepristone was established. Of note, MIFEPRX is given only as a single dose of 600 mg to healthy young females. Since Korlym will be used for the chronic treatment of hypercortisolemia in a different population of patients (patients with Cushing's syndrome), thus, it does not appear hat the safety findings associated with a single dose of Mifeprex are particularly relevant to the current application.

9 Appendices

9.1 Literature Review/Reference

9.1.1 Literature Review

Fourteen reports of mifepristone use in patients with Cushing's syndrome have been published between 1985 and 2009. These publications included total of 51 patients. One publication presented the results of PD study conducted in 7 subjects with CS (Bertagna et al, 1986). Thirteen publications include single case report (11 reports) or small case series reports (20 patients (Castinetti et al, 2009) and 11 patients (Chrousos et al, 1989), respectively); some patients were included in more than one report (Nieman et al, 1987; Nieman et al, 1985; Chrousos et al, 1989). Overall, a total of 44 patients with Cushing's syndrome who were treated with mifepristone 200-2000 mg/day (or 5-30 mg/kg/day) for up to 24 months were presented in 13 publications. The majority of reported patients had ACTH-dependent Cushing 's syndrome (20/44 patients), 19 patients had ACTH-independent Cushing's Syndrome and 5 patients had Cushing's syndrome of unspecified etiology. Ectopic ACTH-secreting tumors and adrenal carcinoma were the most frequent causes of Cushing's syndrome in these patients (14/44 and 17/44 patients, respectively). All, but two patients were adult, 20-64 years. Two pediatric patients were included in these publications: 13 years and 27 months old. These published reports are summarized next.

Single- or two-cases studies
Cushing's disease
1) Chu, JW et al. Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486). J Clin Endocrinol Metab 2001; 86:3568-3573.
This report includes a 51-year old male who was diagnosed with ACTH-secreting pituitary macroadenoma and was treated with mifepristone for 8 months. The patient's Cushing's features included DM, hypertension, cardiomyopathy, psychosis, somnolence, and muscle atrophy. He was initially treated with surgery and radiotherapy unsuccessfully. Ketoconazole was initiated later, but was also ineffective; the patient could not tolerate metyrapone too. Mifepristone was started at dose 400 mg/day (6 mg/kg/day); the dose was advanced to 2000 mg/day within next 8 months (25 mg/kg/day). Overall treatment with mifepristone was continued for 18 months. Patient responded to mifepristone therapy: he had an improvement in heart failure (from NYHA class IV to class I), triglyceridemia, and muscle strength. Psychotic depression resolved. Glycemic control significantly improved in this patient: HgbA1c decreased from 10.4% to 6.9%, antidiabetic medications were discontinued. Patient developed two adverse events during mifepristone treatment: hypokaliema and adrenal insufficiency that occurred at month 10. Hypokaliemia was successfully treated with spironolactone; adrenal insufficiency was treated with glucocorticoids and mifepristone dose reduction. Authors concluded that patient's Cushing's syndrome symptoms eventually improved due to the delayed effect of radiation.

Ectopic ACTH secreting tumors

2) Bilgin et al. Treatment of severe psychosis due to ectopic Cushing's syndrome. J Endocrinol Invest 2007; 30:776-779.

This a single case report of 46-yr-old woman with ectopic Cushing's syndrome due to ACTH-producing lung carcinoma who was treated with a combination of mifepristone and etomidate. The tumor was inoperable, and a patient was initially treated with chemotherapy and radiotherapy. As a consequence of severe hypercortisolemia, patient developed severe psychosis, obesity, muscle atrophy, hirsutism, striae, lower extremity edema, hypokalemia, and metabolic alkalosis. Cortisol and ACTH levels were elevated to 4.2 mumol/L (normal range 0.17-0.61 mumol/L) and 788 ng/mL (normal range 7-50 ng/l), respectively. Because of severe psychosis that was unresponsive to antipsychotic therapy, patient was sedated and intubated; intravenous etomidate 0.2 mg/kg/hr, oral mifepristone 8 mg/kg daily and dexametahsone 2 mg/day (to avoid adrenal insufficiency) were initiated simultaneously. Spironolactone and potassium were added for the hypokalemia treatment. In 4 days patient's condition improved: hypokalemia and metabolic alkalosis resolved, ACTH and cortisol levels decreased. Psychosis resolved and patient was successfully extubated and continued mifepristone treatment 800 mg/day. Etomidate was discontinued and dexametahsone was decreased to 1 mg/day. The ACTH and cortisol levels increased after discontinuation of etomidate, thus mifepristone dose was increased to 1600 mg/day within 10 days even though signs of psychosis did not reoccur. The initial decrease in ACTH and cortisol levels was most likely due to the inhibition of cortisol synthesis by etomidate; the subsequent increase in ACTH and cortisol levels simultaneously with the improvement of patient's symptoms was most likely due to the mifepristone blockade of cortisol receptors. Thus patient most likely did not need dose adjustment at that time. The patient was discharged home, but shortly died due to the progression of the underlying lung carcinoma.

3) Cassier et al. Mifepristone for ectopic ACTH secretion in metastatic endocrine carcinomas: report of two cases. Eur J Endocrino2008; 158:935-93.

This publication included two case reports of adult patients with ectopic ACTH-producing tumors and severe Cushing's syndrome successfully treated with mifepristone.

Case 1

First case presented a 46-year-old female with a pancreatic gastrinoma with liver metastasis diagnosed 10 years prior to this publication. Patient underwent chemotherapy, and multiple surgeries for the treatment of the disease. Subsequently, patient developed diabetes, facial swelling, muscle weakness, lower extremities edema, hypertension, elevated ACTH to 100 ng/l (normal < 24 ng/l) and cortisol levels to 700 nmol/L (normal < 550 nmol/L), and was diagnosed with ectopic Cushing's syndrome. Medical therapy with aminoglutetimide was poorly tolerated; treatment with rosiglitazone was ineffective. Thus, mifepristone 400 mg daily was initiated and resulted in an improvement of diabetes with a discontinuation of insulin treatment, facial and truncal swelling within three months. Patient had persistent hypokalemia (3.1 mmol/L) that was present before starting mifepristone and was resistant to the oral potassium supplementation and spironolactone; the hypokalemia did not worsen during mifepristone treatment. Diabetes, hypertension, and hypokalemia recurred after 10 months of

mifepristone therapy, thus the dose of mifepristone was gradually increased to 1600 mg. This dose escalation improved the glycemic control again, but not hypertension, edema, or hypokalemia. Patient eventually underwent bilateral adrenalectomy; hypertension, diabetes and hypokalemia resolved after surgery. Authors indicated that no side effects were noticed on liver, kidney and thyroid function tests.

Case 2
The second case describes a 37-year-old female patient who was diagnosed with lung carcinoid that was removed. In spite of successful surgery, patient was diagnosed with liver metastases that contained carcinoid cells and underwent chemotherapy. Subsequently, patient developed diarrhea and hypokalemia and was started on Sandostatin LP 20 mg monthly to treat diarrhea; the drug continued for 4 months. Patient developed asthenia, weigh gain, hypertension, hypertrichosis, and facial swelling; ACTH (114 ng/L) and cortisol (998 nmol/L) levels were elevated. MRI of pituitary did not reveal any tumors, and patient was diagnosed with ectopic Cushing's syndrome. Treatment with Mifepristone 400 mg/day was initiated; facial swelling, muscular weakness, hypertrichosis, and skin hematomas improved within three months. Glucose levels also decreased and HbAlC normalized. Hypokalemia (1.9-3.2 mmol/L) and hypertension (160/100 mm Hg) remained resistant to mifepristone, potassium supplementation (up to 9600 mg/day) and spironolactone (75 mg/day). Patient eventually underwent bilateral adrenalectomy; hypertension and hypokalemia resolved after surgery. Author concluded that mifepristone may control partially signs and symptoms of hypercortisolemia in patients with ectopic CS; hypertension and hypokalemia have to be controlled by the other means.

4) Nieman et al. Antiglucocorticoids: Basic and clinical studies. (In Recent Advances in Adrenal Regulation and Function. R. D'Agata, and G.P. Chrousos, editors. New York: Raven Press. 1987. 235-258.
The authors stated that they have treated six patients with mifepristone at oral doses of 5-20 mg/kg/day, but described in details only two patients "who have had long-term treatment with mifepristone". The doses of mifepristone were not specified in these two patients. The first patient was a 25 years old male with metastatic ectopic ACTH-secreting bronchial carcinoid. The second patient was a 30 year-old male with an occult ectopic ACTH-producing tumor. Both patients presented with moon face, obesity, hypertension, hypokaliemic alkalosis, glucose intolerance, and loss of libido with suppressed gonadotropins and total and free testosterone levels, elevated ACTH and cortisol levels. The first patient also had a severe depression, and the second patient presented with oral candidiasis. Mifepristone treatment resulted in clinical improvement of facial plethora, moon face, obesity, peripheral edema, muscle strength, and libido in both patients. Oral candidiasis in the first patient and depression in the second patient resolved. Both patients had an improvement in glucose tolerance and blood pressure control; antihypertensive medications were discontinued. Hypokalemia resolved and potassium supplementation was stopped.

5) Nieman et al. Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. J Clin Endocrinol Metab 1985; 61:536-540.

This is a report of 25-year old male patient with Cushing's syndrome due to ectopic ACTH secretion by a bronchial carcinoid. Patient developed depression diminished cognitive abilities, muscle weakness, metabolic alkalosis, obesity, dorsocervica1 fat pad, moon facie and diabetes as a result of hypercortisolemia. Mifepristone was administered in increasing doses of 5, 10, 15 and 20 mg/kg/day for a 9-week period. Patient's signs and symptoms of Cushing's syndrome including dorsocervical fat pad, obesity, moon facies improved; BP decreased from 200/120 mmHg to 140/90 mmHg, depression resolved, and libido returned. Fasting and post-OGTT glucose, LH and TSH levels normalized. No adverse events with mifepristone treatment were observed.

6) Oosterhuis et al. Life-threatening Pneumocystis j jiroveci pneumonia following treatment of severe Cushing's syndrome. Neth J Med 2007; 65:215-217.
This paper presented two case reports that mostly focused on the description of the development of life-threatening P. jiroveci pneumonia in patients with Cushing's syndrome, and does not present mifepristone efficacy and/or safety findings.

Case 1
A 62-year-old woman had a 3-year history of Cushing's syndrome due to ectopic ACTH production from pulmonary carcinoid with the following features: hypertension, hirsutism, a moon face, visual disturbances, muscle weakness in the lower extremities, diabetes, hypokalemia, and elevated levels of ACTH, cortisol, and urine free cortisol. Spironolactone and mifepristone 400 mg/day were started in anticipation of pulmonary surgery. A few days later the patient developed severe hypoxia with bilateral infiltrates on X-Ray; P. jiroveci pneumonia was suspected. Bronchial lavage was negative for the pathogen, but treatment with high-dose trimethoprim-sulphamethoxazole improved patient's respiratory status. A few weeks later the patient underwent a successful left upper lobectomy.

Case 2.
A 57-year-old woman was diagnosed with pancreatic ectopic ACTH-producing tumor with liver metastasis. She developed malaise, moon face, alopecia, muscle weakness, striae, obesity hypertension, diabetes and elevated plasma ACTH and cortisol, and hypokalemia. Medical treatment with ketoconazole was started, followed by mifepristone 400 mg/day and spironolactone. Two days later patient developed respiratory failure and was diagnosed with P. jiroveci pneumonia, thus trimethoprim-sulphamethoxazole was administered. Mifepristone was stopped and glucocorticoids were started for the hypotension treatment. The pulmonary symptoms improved and the patient subsequently underwent bilateral adrenalectomy.

<u>ACTH- Dependent Cushing's of Unknown Origin</u>
7) Beaufrere et al. RU 486 administration in a child with Cushing's syndrome Lancet 1987; 2:217.
This single case report presents a pediatric case of ACTH-dependent Cushing's syndrome of unknown origin. A 27 month-old girl had a 12-month history of growth failure, obesity, typical Cushingoid appearance, severe hypertension, fasting hyperglycemia, osteoporosis, and elevated cortisol and ACTH levels. Mifepristone was initiated orally at a dose of 25 mg three

times daily (5 mg/kg), and was increased over 3 weeks to 100 mg three times daily. During the treatment blood pressure decreased and glucose normalized. No side-effects were noted. Mifepristone was discontinued two months later; patient remained in a remission 10 months later. No adverse effects were reported. Interestingly, the authors reported that ACTH and cortisol levels decreased during mifepristone treatment: ACTH decreased from 2016 pg/mL to 310 pg/mL, cortisol decreased from 3845 nmol/L to 584 nmol/L during mifepristone treatment. Levels remained normal after discontinuation of the drug (< 15 pg/mL and 122 nmol/L, respectively). It is not typical for the ACTH and cortisol levels to decrease during treatment with glucocorticoid receptor blocker; the levels usually remain elevated. Thus, the author concluded that most likely improvement in patient's condition is due to the cyclic nature and /or spontaneous cure of the disease and not to the effect of mifepristone itself.

ACTH-Independent Cushing's Syndrome
Adrenal Carcinoma

8) Contreras et al. Adrenal cancer: tumor regression with ketoconazole or mifepristone (ru 486): in vivo and in vitro evidence supporting tumoral hormone dependency. In 69th Annual Endocrine Society Meeting, Indianapolis, 1987.

This article describes a patient with inoperable, metastatic adrenal carcinoma who was treated with mifepristone 30 mg/kg/day. Within four months of the therapy, Cushingoid features resolved. Interestingly, authors reported that the size of liver metastases also reduced in two months after initiation of the treatment with mifepristone and liver function tests normalized. Moreover, urine cortisol concentrations that initially increased from 740 mcg/day to 2, 650 mcg/day, decreased subsequently to 100 mcg/day. The decrease in cortisol levels is not typically seen with mifepristone use; the levels remain elevated during the mifepristone treatment. Patient also developed the following adverse events: adrenal insufficiency treated by a mifepristone dose reduction to 20 mg/kg/day, edema and polymenorrhea (after 2 months of treatment with mifepristone). In conclusion, the reduction of metastasis sizes with improvement in liver function tests may be due to the effect of the other treatment modalities such as radiation and chemotherapy or spontaneous tumor regression that decrease cortisol levels. Thus, the observed improvement in patient's status may be due to diminished production of cortisol by tumor and not because of mifepristone treatment.

9) Donkier et al. Late recurrence of operated adrenocortical carcinoma: atrial natriuretic factor before and after treatment with mitotane (Surgery 1989; 105:690-692).

Authors presented a case of a 62-year-old man with adrenal carcinoma who underwent a successful surgery in past. Fifteen years later, patient presented with tumor recurrence and typical Cushing's features including diabetes, hypertension and a Cushingoid appearance (obesity and wasting of leg muscles); cortisol levels were elevated. The patient was started on mifepristone 400 mg/day. Hypokaliemic alkalosis and diabetes improved, and patient continued treatment with mifepristone. Unfortunately, 8 months later, the effects of cortisol overproduction overcome the glucocorticoid receptor blockade, and patient's symptoms worsened. The cortisol levels increased to 1035 nM/l at the 8-month assessment from 690 nm/l at baseline; no ACTH was measured during the study. Mifepristone therapy was discontinued, and treatment with mitotane at 2-8 g/day was initiated. Patient responded to mitotane therapy

well with resolution of hypokaliema and diabetes and decrease in tumor size, but developed adrenal insufficiency.

10) Van der Lely et al. Rapid reversal of acute psychosis in the Cushing syndrome with the cortisol-receptor antagonist mifepristone (RU 486). Ann Intern Med 1991; 114:143-144.
Authors presented two cases of patients with Cushing's syndrome caused by adrenal carcinoma who presented with severe psychosis due to hypercortisolemia and were treated with mifepristone.

Case 1
A 43-year-old man presented with Cushing's syndrome due to adrenal cancer with liver and lungs metastases. Patient was treated with mitotane for 2 weeks, but developed acute and severe psychosis. Thus, treatment with 800 mg of mifepristone once a day was initiated. Psychiatric symptoms improved within 12 hours after the initiation of treatment with mifepristone, all mental abnormalities resolved within 24 hours. Patient continued treatment with mifepristone, but developed hypoglycemia and eosinophila. Thus, the daily dose of mifepristone was lowered to 400 mg. Other signs and symptoms of Cushing's syndrome started to improve, but patient died 2 weeks later due to the tumor progression. No adverse events associated with mifepristone were reported in this paper, but, in this reviewer opinion, such symptoms as hypoglycemia and eosinophila might be suggestive of adrenal insufficiency.

Case 2
A 32-year-old woman with adrenal carcinoma had persistent Cushing's syndrome features and elevated cortisol levels in spite of 7-week therapy with mitotane. Patient also developed paranoid psychosis, thus treatment with mifepristone 400 mg/day was initiated. Psychotic symptoms improved within 24 hours, and resolved completely within three days; the symptoms did not reoccur during the last 2 months of her life. Other signs and symptoms of Cushing's syndrome also improved during the treatment with mifepristone. Authors did not specify the duration of mifepristone therapy, but stated that no evidence of adrenal insufficiency (hypoglycemia or eosinophila) was observed.

Unspecified Cushing's Syndrome
11) Newfield et al. Long term mifepristone (RU486) therapy resulting in massive benign endometrial hyperplasia. Clin Endocrinol (Oxl) 2001; 54:399-404.
The author described a case of pediatric patient with Cushing's syndrome. A 7-year old girl presented with a progressive weight gain. She also developed moon facies, buffalo hump, supraclavicular fullness, and violaceous striae over the next two years. Additionally, patient experienced multiple spine fractures at age 11. In spite the fact that cortisol levels were within normal limits, the authors assumed that the above features were typical of a glucocorticoid excess, and, thus, initiated treatment with mifepristone 400 mg per day when patient was 14 years old. The patient's striae, weight gain, and buffalo hump improved, but patient experienced vaginal bleeding. She responded well to the treatment with oral contraceptive pills, but mifepristone was discontinued in 6 months. A second 6-month course with mifepristone treatment was started nine months later and was complicated by an enlarged

uterus with thin myometrium after five months of treatment. Mifepristone was discontinued, patient was treated with medroxyprogesterone; histology was consistent with simple endometrial hyperplasia typically seen with unopposed estrogen effect.

Case Series
Two small case series are presented below.

12) Castinetti et al. Merits and pitfalls of mifepristone in Cushing's syndrome. Eur J Endocrinol 2009; 160:1003-1010).
This largest case series included 22 patients with Cushing's syndrome: 4 patients with Cushing's disease, 3 patients with ectopic ACTH-producing tumors (thymic carcinoma (1 patient), small cell lung cancer (2 patients), 12 patients with adrenal carcinoma and one patient with adrenal hyperplasia. Of 22 patients, 14 patients underwent unsuccessful surgery (2 patients with Cushing's disease, 3 patients with ectopic ACTH-producing tumors, and 9 patients with adrenal carcinoma). One patient with Cushing's disease underwent surgery and radiation therapy; two patients with pituitary tumor were not candidates for surgery. Eleven of 12 patients with adrenal carcinoma were treated with chemotherapy and/or mitotane. Medical therapy with ketoconazole (6 patients), metyrapone (3 patients), etomidate (1 patient) or mitotane (1 patient) also been tried unsuccessfully or was discontinued due to poor tolerance of the drugs. The median starting dose of mifepristone was 600 mg/day (range 300- 600 mg a day) in patients with Cushing's disease and 400 mg/day (range 200-1000 mg) in patients with ectopic Cushing's syndrome and adrenal cancer. Median maximum doses were 700 mg/day (range 600-1200), 600 mg/day (range 600- 800 mg) and 600 mg/day (400-2000), respectively. One patient with ectopic ACTH-producing tumor was treated concomitantly with metyrapone. The duration of the treatment with mifepristone was the longest in patients with pituitary tumors (9 months; range 0.5-24 months) and the shortest in patients with more aggressive tumors such as ectopic ACTH-producing and adrenal cancer tumors (2 months (range 1-21 months) and 2 months (range 5 days-6 months), respectively). One patient with bilateral adrenal hyperplasia was treated with mifepristone 600 mg/day for six months.
Clinical signs of hypercortisolemia improved in 15 patients: in 3/4 patients with pituitary tumors, in 3/3 patients with ectopic ACTH-producing tumors, in 8/12 patients with adrenal cancer and in one patient with adrenal hyperplasia. Four of 7 patients who had diabetes at baseline improved glycemic control; insulin dose was decreased and/ or discontinued in 2 patients. Patient with adrenal hyperplasia had HbA_{1C} levels decreased from 7.1% to 6.4%. Blood pressure decreased in 6/ 10 patients with cortisol-induced hypertension at baseline: in 5 patients with adrenal cancer and in one patient with adrenal hyperplasia. Additionally, psychiatric symptoms improved in 1/ 2 patients with adrenal cancer who presented with psychosis. The only adverse events that were reported in this publication were hypokalemia and hypertension. Hypokalemia occurred or worsened in 12 patients; hypertension developed in 3 patients and was associated with hypokalemia. Mifepristone was discontinued in 13 patients because of tumor progression and/or hypokalemia (2 patients with ectopic ACTH-producing tumor), resistant hypokalemia (1 patient with adrenal cancer), deaths or tumor progression (8 patients with adrenal cancer) and because of lack of significant benefit (2 patients with adrenal cancer).

13) Chrousos et al. Clinical applications of RU 486, a prototype glucocorticoid and progestin antagonist. New York: Raven Press, 1989; 273-284.
Eleven patients with Cushing's syndrome were treated with mifepristone. One of these patients is also reported by Nieman et al and was discussed earlier in this section. The dose range of mifepristone was 5 to 22 mg/kg/day. Improvement in Cushing's syndrome signs and symptoms was observed in 7/11 patients: Cushingoid phenotype, depression, and hypertension improved, glucose intolerance, gonadal and thyroid hormone suppression resolved. The remaining four patients discontinued treatment with mifepristone in 3 -14 days after initiation of the treatment due to AEs: hypotension (l patient), P. carinii pneumonia (l patient), severe nausea and prostration (1 patient), and nausea with low cortisol levels (l patient). Other AEs included gynecomastia (2 patients), impotence (1 patient), Hashimoto's thyroiditis (1 patient) and frequent nausea (unspecified number of patients). Author indicated that only two patients developed adrenal insufficiency with hypotension and did not attribute the presence of nausea in other patients to the development of adrenal insufficiency. As per author, no hematologic, dermatologic, renal or liver toxicity was observed in any of the patients.

14) Bertanga et al. Pituitary-adrenal response to the antiglucocorticoid action of RU 486 in Cushing's syndrome. JCEM, 1986; 63: 639-643.
The publication presented results of PD study conducted in 7 subjects with Cushing's syndrome. Seven patients with Cushing's disease received 400 mg/day of mifepristone for 3 days; serial urine and blood samples for ACTH and cortisol were collected thereafter. The results of the study demonstrated that mifepristone induce a delayed and prolonged pituitary-adrenal response in Cushing's disease; in patients with non-pituitary-dependent Cushing's syndrome, mifepristone induced no variation in adrenal activity. This study was not designed to evaluate the efficacy or safety of mifepristone, although patients were monitored for the possible side effects during the study. Authors stated that no patients had changes in vital signs, WBC counts, fasting glucose, electrolytes or plasma insulin. Two patients were symptomatic during the study: one patient developed headache and nausea 3 days after the last dose of mifepristone and one patient became lethargic on the second day of mifepristone administration. Blood pressure, glucose and electrolytes levels were normal in both patients. Both patients received injection of dexamethasone that induced remission immediately. Authors concluded that, even though there was no firm evidence that these patients developed adrenal insufficiency, the possibility of adrenal insufficiency could not be ruled completely.

9.1.2 References

1. Standards of medical care in diabetes, 2011. Diabetes care 34 Suppl 1:S11-61
2. The Seventh Report on the Joint National Committee on Prevention, Detection, Evalaution, and Treatment of High Blood Pressure. In. Bethesda: National Heart, Lung, and Blood Institute (US), 2004
3. Alexandraki KI, Kaltsas GA, Isidori AM, Akker SA, Drake WM, Chew SL, Monson JP, Besser GM, Grossman AB 2009 The prevalence and characteristic features of

cyclicity and variability in Cushing's disease. European journal of endocrinology / European Federation of Endocrine Societies 160:1011-1018
4. Beaufrere B, de Parscau L, Chatelain P, Morel Y, Aguercif M, Francois R 1987 RU 486 administration in a child with Cushing's syndrome. Lancet 2:217
5. Bertagna X, Bertagna C, Laudat MH, Husson JM, Girard F, Luton JP 1986 Pituitary-adrenal response to the antiglucocorticoid action of RU 486 in Cushing's syndrome. The Journal of clinical endocrinology and metabolism 63:639-643
6. Bhattacharyya A, Kaushal K, Tymms DJ, Davis JR 2005 Steroid withdrawal syndrome after successful treatment of Cushing's syndrome: a reminder. European journal of endocrinology / European Federation of Endocrine Societies 153:207-210
7. Bilgin YM, van der Wiel HE, Fischer HR, De Herder WW 2007 Treatment of severe psychosis due to ectopic Cushing's syndrome. Journal of endocrinological investigation 30:776-779
8. Biller BM, Grossman AB, Stewart PM, Melmed S, Bertagna X, Bertherat J, Buchfelder M, Colao A, Hermus AR, Hofland LJ, Klibanski A, Lacroix A, Lindsay JR, Newell-Price J, Nieman LK, Petersenn S, Sonino N, Stalla GK, Swearingen B, Vance ML, Wass JA, Boscaro M 2008 Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. The Journal of clinical endocrinology and metabolism 93:2454-2462
9. Bruno O 2010 Clinical Features of Cushing's Syndrome. In: Bronstein M ed. Cushing's Syndrome:Pathophysiology, Diagnosis and Treatment (Contemporary Endocrinology): Humana Press; 60
10. Cassier PA, Abou-Amara-Olivieri S, Artru P, Lapalus MG, Riou JP, Lombard-Bohas C 2008 Mifepristone for ectopic ACTH secretion in metastatic endocrine carcinomas: report of two cases. European journal of endocrinology / European Federation of Endocrine Societies 158:935-938
11. Castinetti F, Fassnacht M, Johanssen S, Terzolo M, Bouchard P, Chanson P, Do Cao C, Morange I, Pico A, Ouzounian S, Young J, Hahner S, Brue T, Allolio B, Conte-Devolx B 2009 Merits and pitfalls of mifepristone in Cushing's syndrome. European journal of endocrinology / European Federation of Endocrine Societies 160:1003-1010
12. Chrousos G, nieman, LK, Udelsman, R, Kawai, S, Loriaux, L 1989 Clinical applications of RU 486, a prototype glucocrticoid and progestin antagonist. New York: Raven Press:273-274
13. Chu JW, Matthias DF, Belanoff J, Schatzberg A, Hoffman AR, Feldman D 2001 Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486). The Journal of clinical endocrinology and metabolism 86:3568-3573
14. Clayton RN, Raskauskiene D, Reulen RC, Jones PW 2011 Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. The Journal of clinical endocrinology and metabolism 96:632-642
15. Contreras P, Caviedas, R, Rojas, R, Lopez, M 1987 Adrenal cancer: tumor regression with ketoconazole or mifepristone (ru 486): in vivo and in vitro evidence supporting tumoral hormone dependency. 69th Annual Endocrine Society Meeting, Indianapolis, 1987

16. Donckier JE, Michel LA, Berbinschi A, De Coster PM, De Plaen JF, Ketelslegers JM, Buysschaert M 1989 Late recurrence of operated adrenocortical carcinoma: atrial natriuretic factor before and after treatment with mitotane. Surgery 105:690-692
17. Etxabe J, Vazquez JA 1994 Morbidity and mortality in Cushing's disease: an epidemiological approach. Clinical endocrinology 40:479-484
18. Heikinheimo O, Ranta S, Grunberg S, Lahteenmaki P, Spitz IM 1997 Alterations in the pituitary-thyroid and pituitary-adrenal axes--consequences of long-term mifepristone treatment. Metabolism: clinical and experimental 46:292-296
19. Johanssen S, Allolio B 2007 Mifepristone (RU 486) in Cushing's syndrome. European journal of endocrinology / European Federation of Endocrine Societies 157:561-569
20. 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
21. Loriaux L 2001 The Adrenal Glands. In: Becker K ed. Principles and practice of Endocrinology and metabolism: Lippincott Williams & Wilkins; 736
22. Malik M Facts, fancies and follies of drug-induced QT/QTc interval shortening. British journal of pharmacology 159:70-76
23. Newell-Price J, Bertagna X, Grossman AB, Nieman LK 2006 Cushing's syndrome. Lancet 367:1605-1617
24. Newfield RS, Spitz IM, Isacson C, New MI 2001 Long-term mifepristone (RU486) therapy resulting in massive benign endometrial hyperplasia. Clinical endocrinology 54:399-404
25. Nieman L, Udelsman, R, Loriaux, DL, Chrousos, GP 1987 Antiglucocorticoids: Basic and clinical studies. In: D'Agata R, Chrousos, GP ed. Recent Advances in Adrenal Regulation and Function: New York: Raven Press; 235-258
26. Nieman L 2010 Cushing's Syndrome. In: Hall J, Nieman, LK ed. Handbook of Diagnostic Endocrinology Humana Press; 67-82
27. Nieman LK 2002 Medical therapy of Cushing's disease. Pituitary 5:77-82
28. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, Montori VM 2008 The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. The Journal of clinical endocrinology and metabolism 93:1526-1540
29. Nieman LK, Chrousos GP, Kellner C, Spitz IM, Nisula BC, Cutler GB, Merriam GR, Bardin CW, Loriaux DL 1985 Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. The Journal of clinical endocrinology and metabolism 61:536-540
30. Oosterhuis JK, van den Berg G, Monteban-Kooistra WE, Ligtenberg JJ, Tulleken JE, Meertens JH, Zijlstra JG 2007 Life-threatening Pneumocystis jiroveci pneumonia following treatment of severe Cushing's syndrome. The Netherlands journal of medicine 65:215-217
31. Pivonello R, De Martino MC, De Leo M, Lombardi G, Colao A 2008 Cushing's Syndrome. Endocrinology and metabolism clinics of North America 37:135-149, ix

32. Shoupe D, Mishell DR, Jr., Page MA, Madkour H, Spitz IM, Lobo RA 1987 Effects of the antiprogesterone RU 486 in normal women. II. Administration in the late follicular phase. American journal of obstetrics and gynecology 157:1421-1426
33. van der Lely AJ, Foeken K, van der Mast RC, Lamberts SW 1991 Rapid reversal of acute psychosis in the Cushing syndrome with the cortisol-receptor antagonist mifepristone (RU 486). Annals of internal medicine 114:143-144
34. Vance ML 2005 Pituitary radiotherapy. Endocrinology and metabolism clinics of North America 34:479-487.

9.2 Labeling Recommendations

The labeling recommendations were not finalized at time of the initial review. Thus, a full summary and line-by-line labeling review will be added as an addendum to this Review.
At present time, I am recommending that the *Indications and Usage* Section of Korlym label specifies that the Korlym (mifepristone) is indicated to treat the clinical and metabolic effects of hypercortisolemia in patients with endogenous Cushing's syndrome and glucose intolerance or diabetes mellitus induced by hypercortisolemia.
Additionally, I am recommending adding adrenal insufficiency to the box warning. Adrenal insufficiency is a serious adverse event and may be lethal if left untreated.
The above recommendations are those of the primary reviewer and do not constitute the final decision.

In addition, Clin. Pharm reviewer recommends adding the following precautions:
- Maximum dose for patients with hepatic impairment should not exceed 600 mg.
- Use of simvastatin or lovastatin is 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.
- Use of strong inhibitors of CYP3A is contraindicated.
- Mild to moderate inhibitors of CYP3A require no dose adjustment of Korlym.
- Use of moderate inhibitors of CYP3A4 should be avoided.

9.3 Advisory Committee Meeting

There were no Advisory Committee Meetings for this application

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARINA ZEMSKOVA
01/22/2012

DRAGOS G ROMAN
01/27/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202107 **Applicant: Corcept Therapeutics Stamp Date:**

Drug Name: (b) (4) **(mifepristone)** **NDA/BLA Type:**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			The general format used by sponsor for this application is a hybrid application. The sponsor has submitted Modules 1 through 5 in paper. Labeling and patients' dataset are submitted in electronic CTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?			X	See above
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?		X		Sponsor and Agency agreed during pre-NDA meeting (September 14, 2010) that only Summary of Clinical Efficacy and Summary of Clinical Safety will be submitted since the application includes a single clinical (and an extension) study.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		See above
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			The sponsor indicated that this application is a 505(b)(2). The reference drug is Mifeprex (NDA 20-687)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: C-1073-400 Study Title: An Open-label Study of the Efficacy and Safety of CORLUX (mifepristone) in the Treatment of the Signs and Symptoms of Endogenous Cushing's Syndrome Sample Size: 50 Arms: Single arm Location in submission: Module 5	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: An Open-label Study of the Efficacy and Safety of CORLUX (mifepristone) in the Treatment of the Signs and Symptoms of Endogenous Cushing's Syndrome Indication: Cushing's syndrome	X			As was discussed during the initial review of IND 76480 on 9 September, 2007, the single study with an accompanying review of the literature provides reasonable basis for NDA submission and the open-label design of the study is acceptable
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Same as above
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			The primary endpoints in the pivotal study were changes in AUC glucose and diastolic blood pressure as was advised by the Division during the initial review of IND 76480 on 9September, 2007.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	All studies were conducted in US.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Sponsor conducted QT study, C-1073-300, in healthy volunteers, and submitted the results of the study
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			Sponsor incorporated ophthalmological evaluation and endometrial thickness evaluation in studies C-1073-400 and C-1073-415, and C-1073-425 (ophthalmological evaluation only) as per Division's request. Additionally, Sponsor conducted C-1073-425 evaluating the effect of mifepristone on HDL level in healthy volunteers.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Orphan drug. The applicant was exempted from pediatric assessment and has provided the appropriate documentation.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			The applicant submitted dataset in SAS format as has been requested by Agency
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			Same as above
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			Same as above
34.	Are all datasets to support the critical safety analyses available and complete?	X			Same as above
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comments to be sent to Sponsor:
Please submit or indicate where the following information about the patients enrolled in study C-1073-400 can be found in the current submission:

1. Previous medical treatment of hypercortisolemia in patients with all causes of Cushing's syndrome:
   -how many patients were naïve to the medical treatment prior to the study enrollment
   -how many patients were treated medically and were subsequently "washed out" of medical treatment prior to the study enrollment
   - if patients were treated medically in past, what antiglucocorticoid drugs were used , in general, and by patient
   - if patients were treated medically in past, how many of them failed drug therapy
2. Previous radiation treatment of patients with Cushing's disease:
   - what time period has elapsed in each patient since last date of radiation treatment (years/months/ days)

Marina Zemskova, M.D.	6/2/2011
Reviewing Medical Officer	Date
Dragos Roman MD	6/2/2011
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARINA ZEMSKOVA
06/09/2011

DRAGOS G ROMAN
06/09/2011