

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202107Orig1s000**

**PHARMACOLOGY REVIEW(S)**

**PHARM/TOX SUPERVISORY MEMO**

Date:	7 Feb 2012
RE:	Korlym NDA 202107, 505(b)(2) application
Sponsor:	Corcept Therapeutics
Drug/Indication	Mifepristone / Hyperglycemia in Cushing's Syndrome

Corcept Therapeutics is seeking approval of Korlym for the treatment of hyperglycemia secondary to metabolic complications of endogenous Cushing's syndrome. Korlym is the proposed trade name for mifepristone which is a receptor antagonist for the glucocorticoid and progesterin receptors. Anti-androgen activity is also a known effect of mifepristone. The intended therapeutic target for the proposed indication is the glucocorticoid receptor, though inhibition of the progesterin receptor is certain to occur at therapeutic drug concentrations.

Corcept cites Mifeprex (NDA 20687) as the listed drug upon which to rely for part of the toxicological assessment of Korlym (i.e., 505b2), specifically the reproductive and developmental studies as described in the Pregnancy and related sections of the approved Mifeprex drug label. Reliance on Mifeprex for this information is scientifically valid based on studies conducted by Corcept that chemically identified Korlym as mifepristone, the same active ingredient in Mifeprex. Further, the toxicological profile of Korlym observed in two-year rodent bioassays and a twelve-month dog assay, along with associated dose-ranging studies, also conducted by Corcept, are consistent with the known pharmacology of mifepristone as a glucocorticoid and progesterin receptor antagonist. Confirmation that the chemical identity and pharmacological/toxicological activity of Korlym is consistent with mifepristone provides sufficient information to bridge to Mifeprex as the listed drug.

As Mifeprex is approved for single-dose use, Corcept was obligated to characterize the chronic toxicology of Korlym in new studies to support the chronic clinical indication sought in Cushing's patients. Thus, the pivotal studies included a twelve-month dog study and two-year bioassays in rats and in mice. As described in Dr. Brundage's review, these animal species did not tolerate mifepristone at doses that were tolerated by human subjects in clinical trials. The absence of endocrine disruption at baseline in the test species likely explains the inability to test doses of mifepristone much above the intended clinical dose. At the doses tested, the observations made were consistent with the anticipated pharmacology and toxicology of an anti-glucocorticoid, anti-progesterin, anti-androgen agent. The extensive and complex hepatic metabolism noted in animals likely underlies the treatment-related liver effects which ranged from hepatocellular enlargement and ALT elevation in rodents and dogs in shorter-term studies to liver adenomas and follicular cell thyroid adenoma and carcinoma in female rats exposed to mifepristone for two years. Complex hepatic metabolism is also seen in human subjects, and periodic transaminase monitoring may be a reasonable safety measure. Within the dosing

limitations discussed above, results of these studies adequately addressed the lack of chronic toxicology data with mifepristone and adequately support, in part, its proposed clinical use in Cushing's patients.

I concur with Dr. Brundage's recommendation of 'approval' for NDA 202107.

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/s/  
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TODD M BOURCIER

02/07/2012

P/T recommends AP

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application Number: 202107  
Supporting Document/s: SDN 1  
Applicant's Letter Date: 15 April 2011  
CDER Stamp Date: 18 April 2011  
Product: Korlym (Mifepristone Immediate-Release Tablet)  
Indication: Reduction of the effects of hypercortisolism in patients with endogenous Cushing's Syndrome  
Applicant: Corcept Therapeutics  
Review Division: Division of Metabolism and Endocrinology Products (HFD-510)  
Reviewer: Patricia Brundage, Ph.D.  
Supervisor/Team Leader: Todd Bourcier, Ph.D.  
Division Director: Mary Parks, M.D.  
Project Manager: Jena Weber

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## 1 Executive Summary

### 1.1 Introduction

This is a 505(b)(2) application for the immediate release (IR) formulation of mifepristone (Korlym<sup>®</sup>) to treat the clinical and metabolic effects of hypercortisolism in patients with endogenous Cushing's syndrome. As an anti-glucocorticoid, mifepristone blocks the biological effects of cortisol centrally and peripherally by competing with cortisol's binding to the glucocorticoid receptor type II (GRII), which reduces the clinical and metabolic manifestations of hypercortisolism.

Mifepristone is approved for the acute indication of pregnancy termination (single dose administration) under NDA 20687 (Danco Laboratories/Population Council). To support the proposed chronic use indication for the treatment of hypercortisolism in patients with endogenous Cushing's syndrome, the sponsor conducted a 12-month toxicology study in the dog and 2-year carcinogenicity studies in the mouse and rat at the request of the Agency. The sponsor is referencing the nonclinical fertility and genotoxicity data in the Mifeprex<sup>®</sup> label (Danco Laboratories/Population Council) as allowed under this 505(b)(2) application.

### 1.2 Brief Discussion of Nonclinical Findings

In addition to the chronic nonclinical studies in the mouse, rat, and dog, the sponsor conducted two *in vitro* hERG studies, pharmacokinetic 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.

Mifepristone is metabolized primarily by CYP3A4 into the metabolites RU42633, RU42848, and RU42698, which are each greater than 10 percent of total drug-related exposure and are pharmacologically active. All three metabolites are formed in humans and all nonclinical species studied.

Repeat dose studies were conducted in the mouse (up to 3 months), rat (up to 3 months), and dog (up to 12 months) in an effort to identify potential toxicities associated with long-term use of mifepristone. Tolerability was exceeded in all species such that evaluating doses much above clinical exposure was not feasible. Consequently, the nonclinical evaluation of mifepristone's toxicity is somewhat limited by the low exposure achieved in animals. Causes for the general signs of moribundity (e.g., reduced activity/ataxia, inappetence, hunched posture and prostration, dehydration) were not clearly established. However, patients with Cushing's syndrome appeared to tolerate mifepristone at doses resulting in moribundity in non-diseased, healthy animals. The difference in the metabolic state of Cushing's patients (e.g., hypercortisolism) versus the healthy animals used in the toxicology studies likely underlies the apparent discordant response to mifepristone.

Despite the dosing limitations in the nonclinical studies, adverse findings not clearly related to the pharmacodynamic activity of mifepristone were identified in the liver, thyroid, and retina of animals.

#### *Liver and Thyroid*

Treatment-related adverse liver effects were noted in all three nonclinical species at doses comparable to clinical exposure. Increased liver weight and hepatocellular hypertrophy,

especially in the rat, are likely due to enzyme induction. However, chronic administration in rats resulted in single cell necrosis, multinucleated hepatocytes, basophilic cell foci, and increased pigmentation. Elevated ALT levels (up to 11X ↑) and hepatocellular pigmentation also occurred in the chronic dog study at exposures equal to or less than clinical exposure. Signs of hepatocellular toxicity in the mouse were also noted at doses marginally above (~5X) clinical exposure. Based on this data, consideration should be given to periodic monitoring of liver transaminase levels in patients exposed to mifepristone for a chronic duration.

Over a two-year dosing period, hepatocellular adenomas, as well as thyroid follicular cell adenomas, carcinomas, and pooled adenomas/carcinomas were identified in female rats. A trend of increased thyroid adenoma with thyroid enlargement was also seen in male rats. The sponsor attributes the hepatocellular and follicular cell tumors to a rat-specific chronic induction of enzyme activity in the liver and subsequent increase in thyroid hormone metabolism resulting in thyroid hyperplasia and eventually neoplasia. Though plausible, the sponsor did not conduct any mechanistic studies to assess thyroid activity/function or hepatic enzyme activity. Moreover, clinically, chronic administration of mifepristone has caused elevations in serum TSH and transient decreases in T4 in Cushing's patients as well as in patients with meningioma. It is unclear to what extent these might be related to liver enzyme induction. There was no treatment-related increase in the incidence of any tumor in mice. However, the 'negative' tumor finding is tempered by the limited exposure ( $\leq 1X$  MRHD of 1200 mg/day; AUC basis) achieved in the study. Overall, the relevance of the liver and thyroid tumors observed in rats to humans is equivocal and cannot be excluded.

#### *Retina*

Treatment-related retinal atrophy in albino rats at clinically relevant exposures (~1X MRHD of 1200 mg/day; AUC basis) appears to be species-specific and therefore not relevant to human subjects chronically exposed to mifepristone. FDA ophthalmology reviewers commented that it is difficult to tell if these nonclinical findings present additional clinical risk beyond that known when glucocorticoids are perturbed in human subjects. Eye exams at entry and every six months for clinical studies longer than 6 weeks in duration requested by the Agency have detected no treatment-related retinal atrophy to date.

#### *Other Observations*

In the mammary gland, there was a marked decrease in fibroadenomas in all dose groups ( $\geq 5$  mg/kg) in the 2-year rat study, but an increase in adenomas/adenocarcinomas up to the mid dose (25 mg/kg;  $< 1X$  MRHD). Although a decrease in body weight at the high dose may have contributed to the broken dose-response for the increase in mammary adenomas/adenocarcinomas, the pharmacology of the drug (i.e., anti-progesterone) does not strongly support a treatment-related increase in mammary tumors.

A concentration-related inhibition of hERG mediated  $I_{Kr}$  current caused by mifepristone and its three major active metabolites, as well as a slight QTc prolongation (6-8 msec) postdose in the chronic dog study at a clinically relevant exposure (~1X the MRHD of 1200 mg/kg; AUC basis) indicate possible cardiac effects. The sponsor conducted a thorough QT study in healthy males, which was determined to be inconclusive by the Agency's Interdisciplinary Review Team.

Other adverse findings of note from the nonclinical program were considered reasonably related to the pharmacodynamic activity (i.e., anti-glucocorticoid, anti-progestin, and

anti-androgen) of mifepristone. Changes in the pituitary and adrenal gland are attributable to perturbations of the HPA axis. However, they are not of significant concern in the Cushing's patient population. Inflammation in the lungs in dogs and pulmonary histiocytosis in rats following chronic administration is also likely due to GR11 blockade.

At exposures below clinical exposure (<1X MRHD), there were adverse effects in the male and female reproductive systems that are attributable to the anti-androgen and anti-progesterone activity of mifepristone. Although these changes do not appear to result in neoplastic lesions, the lack of neoplastic findings is tempered by the limited drug exposure in rats and mice. The reversibility of these findings was not determined, especially in males.

The use of Korlym<sup>®</sup> is contraindicated in women who are pregnant or may become pregnant because of the possibility of pregnancy termination due to mifepristone's potent anti-progestational effect. No nonclinical reproductive studies were required.

### 1.3 Recommendations

#### 1.3.1 Approvability

AP (Approval)

#### 1.3.2 Additional Non Clinical Recommendations

None.

#### 1.3.3 Labeling

The sponsor used language from the approved Mifeprex<sup>®</sup> label (Danco Laboratories/Population Council) to describe the nonclinical genotoxicity and fertility data as allowed under this 505(b)(2) application. The section describing the carcinogenicity data was revised and teratology data from the approved Mifeprex<sup>®</sup> label were added under section 8.1 Pregnancy. Changes/additions to the proposed label are underlined.

(b) (4)

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## 2 Drug Information

### 2.1 Drug

#### CAS Registry Number

84371-65-3

#### Code Name

C1073, RU38486, EP10778

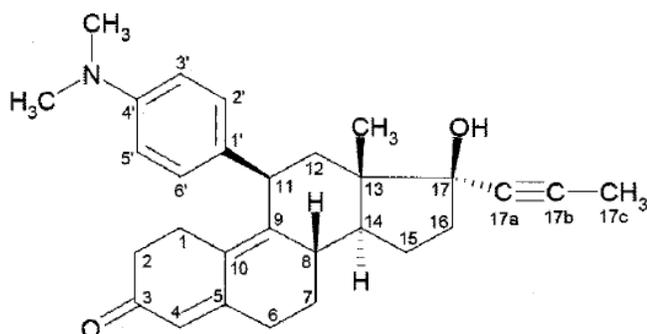
#### Chemical Name

- 11  $\beta$ -(4-dimethylaminophenyl)-17 $\beta$ -hydroxy-17  $\alpha$ -(1-propynyl)estra-4,9-dien-3-one (IUPAC)
- (11  $\beta$ , 17 $\beta$ )-11 ((4-dimethylaminophenyl))-17 $\beta$ -hydroxy-17 -(1-propynyl)-estra-4,9-dien-3-one (chemical abstracts name)

#### Molecular Formula/Molecular Weight

C<sub>29</sub>H<sub>35</sub>NO<sub>2</sub>/429.58 (mifepristone)C<sub>28</sub>H<sub>33</sub>NO<sub>2</sub>/415.57 (RU42633)C<sub>29</sub>H<sub>35</sub>NO<sub>3</sub>/445.59 (RU42698)C<sub>27</sub>H<sub>31</sub>NO<sub>2</sub>/401.54 (RO42848)

#### Structure or Biochemical Description



#### Pharmacologic Class

Glucocorticoid/progesterone receptor antagonist

**2.2 Relevant INDs, NDAs, BLAs and DMFs**

(b) (4)

NDA 20687 (mifepristone; induction of abortion; Danco Laboratories/Population Council; Mifeprex®)  
 DMF (b) (4)

**2.3 Drug Formulation**

Korlym® tablets are immediate release (IR) tablets containing 300 mg of the active component mifepristone. The tablets are light yellow to yellow, oval, film coated, and debossed with "CORCEPT" on one side and "300" on the other. The tablets are produced

(b) (4)

**2.4 Comments on Novel Excipients**

There are no novel excipients in the drug product. Each compendial excipient to be used in the proposed commercial drug product meets the requirements of the respective current USP or NF monograph.

**Excipients (Sponsor's Table)**

Excipient	Amount per Tablet (mg)	% in Core Tablet	Function
(b) (4)			
Sodium Starch Glycolate			(b) (4)
Hydroxypropylcellulose			
Silicified Microcrystalline Cellulose			
(b) (4)			(b) (4)
Sodium Lauryl Sulfate			
(b) (4)			
Sodium Starch Glycolate			(b) (4)
Magnesium Stearate			
Total Core Tablet Weight:	(b) (4) (300 mg mifepristone)		
Film Coating			(b) (4)

(b) (4)

**2.5 Comments on Impurities/Degradants of Concern**

**Impurities**

A limit of NMT (b) (4) was established for individual unspecified impurities, which meets the ICH Q3A(R2) identification threshold based on the maximum daily clinical dose of 1200 mg

mifepristone. A limit of NMT (b) (4) is proposed for the impurity (b) (4) of mifepristone. This equates to a maximum total daily intake of (b) (4) mg based on the maximum 1200 mg/day clinical dose. Although this exceeds the ICH Q3A(R2) impurity qualification threshold, (b) (4) is present in all nonclinical species and humans generally at concentrations similar to or higher than concentrations of the parent drug, mifepristone and is therefore considered qualified.

### Degradants

A limit of NMT (b) (4) was established for individual unspecified degradants, which is in accordance with ICH Q3B(R2).

## 2.6 Proposed Clinical Population and Dosing Regimen

300 mg/day initially and titrated up to 600 mg/day based on assessments of the response and tolerability. Further escalation in 300 mg increments up to a maximum dose of 1200 mg/day may be appropriate in some patients (>60 kg) with increased monitoring for risk factors associated with the drug.

Exposure at the proposed maximum recommended human dose (MRHD) of 1200 mg/day was established in healthy male volunteers administered mifepristone (1200 mg/day) once daily for 7 days (Study C-1 073-19). Exposure at the MRHD was not established in patients with Cushing's syndrome.

### PK Parameters of Mifepristone and its Metabolites following Repeat Dosing (1200 mg/day; 7 days) (Sponsor's Table; Study C-1 073-19)

Renal Function	Analyte	T <sub>max</sub> median (h)	C <sub>max</sub> (ng/mL)	AUC <sub>0-24</sub> (ng*h/mL)	t <sub>1/2</sub> (h)
Normal (N=8)	Mifepristone	1.0	3120 ± 1199	44932 ± 14048	50.3 ± 33.5
	RU 42633	6.0	1666 ± 569	34860 ± 14124	58.5 ± 39.6
	RU 42698	9.0	672 ± 240	13938 ± 5931	53.5 ± 28.8
	RU 42848	10.0	1293 ± 318	28133 ± 6613	60.9 ± 43.8

## 2.7 Regulatory Background

Under NDA 20687, FDA approved mifepristone (Mifeprex<sup>®</sup>) for the termination of early intrauterine pregnancy in September 2000. The FDA-approved regimen consists of taking 600 mg (three 200 mg tablets) of mifepristone orally on Day 1 and 400 µg (two 200 µg tablets) of misoprostol orally on Day 3.

## 3 Studies Submitted

### 3.1 Studies Reviewed

Most studies were previously submitted and reviewed under (b) (4)

Summaries of nonclinical reviews from the INDs are included in this NDA review. Nonclinical studies reviewed/summarized in this submission include:

- Effects on hERG Inhibition Assay using HEK293 Transfected Cells (500331-1/T-013)

- Effects of Mifepristone and Three Metabolites (RU42633, RU42698 and RU42848), on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells (101115.DPT/T-025)
- Protein Binding of C-1073 by Equilibrium Dialysis and Ultracentrifugation (PK-C0173-001)
- Pharmacokinetic Study of C-1073 in Dogs Following an Oral and a Subcutaneous Dose (PK-C0173-005)
- 4-Week Toxicity Study of C1073 in Female Mice (T-003)/GLP/ reviewed under IND59737
- 13-Week Oral Toxicity Study in Mice (T-007)/GLP
- A 28-Day Toxicokinetic Study with C-1073 When Administered Once by Oral Gavage in Sprague-Dawley Rats (T-004)
- A 13-Week Oral Gavage Toxicity Study of C-1073 in the Albino Rat
- 4-Week Oral Toxicity Study of C-1073 in Dogs (PK-007)
- 12-Month Oral Toxicity Study of C1073 in Dogs (T-012)
- 28-day Toxicokinetic Study with C-1073 When Administered Once daily by Oral Gavage to Cynomolgus Monkeys (T-006)
- C-1073 Bacterial Mutation Test (T-009)
- C-1073 Chromosome Aberration test (T-010)
- 104-Week Oral Oncogenicity Study of C1073 in Mice
- A 2-Year Oral Gavage Carcinogenicity Study of C-1073 in the Albino Rat

The following *in vitro* pharmacokinetic studies were submitted to clinical pharmacology for review, but are briefly summarized within this review.

- In Vitro Evaluation of the Binding of Mifepristone and Three Metabolites to Human Plasma Proteins (PK-C1073-002)
- Determination of the Inhibition Potential ( $K_i$ ) of C-1073, RU42633, RU42698, and RU42848 using Human Liver Microsomes (PK-C0173-003)
- Determination of the Inhibition Potential ( $IC_{50}$ ) of C-1073, RU42633, RU42698, and RU42848 using Human Liver Microsomes (PK-C0173-004)
- In Vitro Interaction Studies of Mifepristone (RU486) with Human MDR1, MRP1, MRP2, MRP3, BCRP Transporters, and with Human OATP1B1, OATP1B3, OATP2B1, OCT1, OAT1, and NTCP Uptake Transporters (PK-C0173-006)

### 3.2 Studies Not Reviewed

None

## 4 Pharmacology

In support of this 505(b)(2) new drug application, two safety pharmacology study were conducted to assess the effects of mifepristone on the rapidly activating inward rectifying potassium current ( $I_{Kr}$ ) conducted by hERG channels. No other nonclinical pharmacology

studies were conducted for this 505(b)(2) application. The review relied upon the pharmacology information in the published literature.

#### 4.1 Primary Pharmacology

No new nonclinical primary pharmacology studies were conducted for this 505(b)(2) submission.

##### Mechanism of Action

Mifepristone acts as an antagonist at the progesterone receptor (PR), glucocorticoid receptor type II (GRII), and androgen receptor (AR) (Schreiber et al., 1983; Wagner et al., 1999; Song et al., 2004; Moguilewsky and Philibert, 1985). In binding displacement assays, mifepristone binds with a relatively high affinity to the GRII, PR, and AR (Heikinheimo et al., 1987a; Morgan et al., 2002). Mifepristone binds to the human GRII with an affinity 3-4 times higher than that of dexamethasone and about 18 times higher than that of cortisol (Sartor and Cutler, 1996). Mifepristone's three major metabolites, which obtain relatively high serum levels, also demonstrated binding affinities to the GRII and PR (Heikinheimo et al., 1987a). Mifepristone does not bind appreciably to either the estrogen (ER) or mineralocorticoid receptor (MR) (Moguilewsky and Philibert, 1985; Morgan et al., 2002).

##### Binding Affinity to Human GR, PR, AR, ER $\alpha$ , and ER $\beta$ (Morgan et al., 2002)

compound	GR	PR	AR	ER $\alpha$	ER $\beta$
RU-486	0.24 $\pm$ 0.02	15 $\pm$ 2.6	4.6 $\pm$ 0.41	44% at 10 $\mu$ M	92% at 10 $\mu$ M

Reported as  $K_{is} \pm$  SEM (n=3) in nM or percent inhibition at dose. [3H]-dexamethasone (10 nM) for GR, [3H]-dihydrotestosterone (1 nM) for AR

##### Relative Binding Affinities of Mifepristone and Its Three Metabolites for Human Uterine (Myometrial and Endometrial) PR (Heikinheimo et al. 1987)

Compound	Relative Binding Affinity (%)
Mifepristone	100
Monodemethylated metabolite (RU 42633)	43
Hydroxylated metabolite (RU 42698)	21
Didemethylated metabolite (RU 42848)	15
<i>Progesterone</i>	43
<i>ORG-2058 (potent synthetic progestin)</i>	373

##### Relative Binding Affinities of Mifepristone and Its Three Metabolites for Human Placental GR (Heikinheimo et al. 1987)

Compound	Relative Binding Affinity (%)
Mifepristone	100
Monodemethylated metabolite (RU 42633)	61
Hydroxylated metabolite (RU 42698)	48
Didemethylated metabolite (RU 42848)	45
<i>Dexamethasone</i>	23
<i>Cortisol</i>	9

Several studies have demonstrated that mifepristone functions as an active antagonist at the GR $\beta$  and PR. In addition to competitively inhibiting agonist binding at the GR $\beta$ , mifepristone causes the translocation of the ligand-GR $\beta$  complex into the nucleus where it blocks the agonist-GR $\beta$  complex from interacting with its DNA-target site (Wagner et al., 1999). Mifepristone also has a slow dissociation rate from the intracellular GR $\beta$  relative to other endogenous or synthetic glucocorticoids (Philibert, 1984). At the PR, mifepristone promotes the PR dimerization and binding to specific progesterone response elements (PREs) of target DNA, which effectively competes with binding of agonist-bound PR to the DNA (Leonhardt and Edwards, 2002). However, mifepristone induces an altered conformation in the PR that is distinct from that induced by the hormone agonist rendering the receptor transcriptionally inactive as a result of the recruitment of co-repressors instead of co-activators (Jackson et al., 1997; Zhang et al., 1998; Wagner et al., 1998).

Mifepristone has been shown to inhibit the actions of exogenous and endogenous glucocorticoids and progestins (Philibert et al., 1985). The anti-glucocorticoid activity of mifepristone occurs at slightly higher doses than does the anti-progestational activity (Cadepond et al., 1997; Sitruk-Ware and Spitz, 2003; Peeters et al., 2004). While doses above 1.5 mg/kg interrupted pregnancies (more than 40% of embryos lost) in rats demonstrating its anti-progestational effect, doses of 5 mg/kg and greater effectively blocked the effects of the glucocorticoid dexamethasone (5 mg/day) on body-, adrenal-, spleen-, and thymus-weight (Peeters et al., 2004). The three main metabolites of mifepristone also were shown to have anti-progestational (induction of abortion) and anti-glucocorticoid (inhibition of thymolytic effect) activity (Deraedt et al., 1985).

As an anti-androgen, mifepristone has been shown to cause an interaction between the AR and co-repressors suggesting it could be a selective receptor modulator (Song et al., 2004). According to the approved Mifeprex<sup>®</sup> label, anti-androgenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg. Mifepristone has also been shown to have a low level of AR agonist activity *in vitro* (Kempainen et al., 1992).

### **Drug Activity Related to Proposed Indication**

Cortisol is secreted from the cortical cells of the adrenal glands and is normally under the control of the pituitary hormone ACTH (Glucocorticoid/progesterone receptor antagonist hormone). Production of cortisol by the adrenal gland is stimulated by the ACTH produced by the pituitary. Under normal conditions, pituitary ACTH secretion is then inhibited by increasing levels of cortisol through negative feedback regulation.

In animals (dogs and monkeys) and humans with an intact, functioning hypothalamic-pituitary-adrenal (HPA) axis, mifepristone antagonizes the negative pituitary feedback of cortisol by blocking central GR $\beta$ s (Bertagna et al., 1994; Bertagna et al., 1984; Healy et al., 1983; Spitz et al., 1993). In healthy males, mifepristone (200 mg/day; 8 consecutive days) significantly increased the circulating concentrations of ACTH and cortisol that was reversible within 4 days after the end of treatment (Bertagna et al., 1994). Long-term administration of mifepristone (100 mg/day; 1 year) also produced persistent elevations of ACTH and cortisol; however, the response to CRH and the circadian rhythm of ACTH and cortisol secretion were not affected indicating that the central regulatory mechanisms remain intact (Lamberts et al., 1991). In addition to increases in cortisol and ACTH, long term administration of mifepristone (200 mg/day;  $\geq 1$  year) also caused elevations in TSH, androstenedione, estrone, testosterone and estradiol (Lamberts et al., 1991; Heikinheimo et al., 1997; Heikinheimo et al., 2000).

Cushing's syndrome is a multisystem disorder caused by excess cortisol levels. Cushing's syndrome results from elevated cortisol levels due either to autonomous production of cortisol from the adrenal gland or over-stimulation of the adrenal gland by ACTH.

Endogenous Cushing's syndrome results from the body's increased production of cortisol, whether it is due to an ACTH-dependent or ACTH-independent cause.

With regards to the treatment of Cushing's syndrome, mifepristone acts at the cellular level to prevent the biological effects of cortisol by competing with cortisol's binding to the GR11. Although mifepristone does not decrease cortisol production, it is expected to reduce the clinical impact of hypercortisolism.

#### 4.3 Safety Pharmacology

##### Effects on hERG Inhibition Assay using HEK293 Transfected Cells (500331-1/T-013)

<b>Study #:</b>	500331-1/T-013
<b>Study Report Location:</b>	Module 4; Volume 1.1
<b>Conducting Laboratory and Location:</b>	(b) (4)
<b>Date of Study Initiation:</b>	8 June 2005
<b>GLP Compliance:</b>	Yes
<b>QA Statement:</b>	Yes
<b>Drug, Lot #, and % Purity:</b>	Mifepristone, 70295AA008, 100%

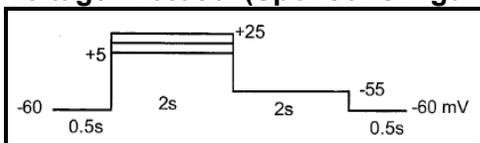
#### Key Study Findings

- Using the whole-cell patch-clamp technique, mifepristone (3-143 µg/mL [ $\sim$ 7-326 µM]) produced no appreciable inhibition of hERG tail potassium current.

#### Methods

HEK293 cells stably transfected with the hERG gene were obtained (b) (4) who modified the cell line to stabilize hERG expression in the presence of lower glutamine levels. The cells were cultured in geneticin and superfused with the hERG/AAG external solution. Recordings were performed in the whole-cell voltage-clamp configuration using a step-pulse protocol. From the holding potential (-60 mV), the cell was depolarized to a maximum value of +25 mV, starting at +5 mV, in 10 mV increments for a duration of 2 seconds. The membrane potential was then returned to -55 mV for 2 seconds before returning to the holding potential. Currents were recorded after a 5-minute equilibration period, following the addition of each mifepristone concentration. The full pulse protocol was applied twice to record two series of activating- and tail-currents; the duplicate currents were averaged. After recording with the vehicle control solution, patched cells (n=7/concentration) were sequentially exposed to increasing concentrations of mifepristone concentrations of 3, 12, 90 and 143 µg/mL ( $\sim$ 7, 28, 210, and 326 µM). *Mifepristone concentrations were selected to cover a range starting at the estimated C<sub>max</sub> from the nonclinical single dose-pharmacokinetic study (3-4 µg/mL) and going up to a concentration at least 30X higher.* E-4031 (500 nM) was used as the positive control. The amplitude of I<sub>Kr</sub> tail current was calculated as the difference between the baseline current (average current recorded before the depolarizing pulse) and the maximum transient current recorded at the beginning of the repolarizing pulse to -55 mV.

**Voltage Protocol (Sponsor's Figure)**



**Experimental Design (Sponsor's Table)**

<b>TEST ARTICLE</b>	Equil'n	Control	3.0 µg/mL	10.0 µg/mL	90.0 µg/mL	150.0 µg/mL	Washout 1	500 nM E-4031	Washout 2
<b>Vehicle control</b>	Equil'n	Control	S/E Concn.1	S/E Concn.2	S/E Concn.3	S/E Concn.4	Washout 1		

**Results**

None of the four concentrations of mifepristone concentrations tested (3, 12, 90, and 143 µg/mL) induced statistically significant changes in the hERG tail normalized current density. However, the positive control E-4031 (500 nM) inhibited significantly the hERG current density recorded by ~50% compared to vehicle control washout confirming the sensitivity of the assay.

**hERG Current Density (Sponsor's Table)**

Treatment	Concentration (µg/mL)		Number of Patched Cells	Net Normalized Current Density (% of Control)	SEM
	Nominal	Measured			
Vehicle Control	hERG External	-	7	100.0	0.0
C-1073	3.0	3.17	7	90.2	5.0
C-1073	10.0	12.3	7	98.5	7.0
C-1073	90.0	89.8	7	102.3	5.7
C-1073	150.0	143.4	7	100.4	5.8
Washout 1	hERG External	-	5	69.8*	4.4
E-4031	500.0 nM	-	3	49.8*	4.8
Washout 2	hERG External	-	3	57.5*	6.9

\*: P ≤ 0.05 when compared to control value

SEM: Standard Error of the Mean

Net: Current density corrected for time-dependent current run-down

Normalized: Net current density data divided by net current density data recorded at the beginning of the experiment, in control condition.

**Effects of Mifepristone and Three Metabolites (RU42633, RU42698 and RU42848), on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells (101115.DPT/T-025)**

**Study #:** 101115.DPT/T-025  
**Study Report Location:** Module 4; Volume 1.1  
**Conducting Laboratory and Location:** (b) (4)  
**Date of Study Initiation:** 5 January 2011  
**GLP Compliance:** Yes (characterization of the positive control was non-GLP)  
**QA Statement:** Yes  
**Drug, Lot #, and % Purity:** Mifepristone, 53041S002/RM-17L08, 100%  
 RU42633, 0498-181-26, 98.65%  
 RU42698, 0539-176-26, 99.5%  
 RU42848, 0638-019-14, 98%

### Key Study Findings

- Mifepristone ( $IC_{50} >10 \mu\text{M}$  [ $>4 \mu\text{g/mL}$ ]) and its metabolites RU42633 ( $IC_{50}$  of  $15 \mu\text{M}$  [ $6 \mu\text{g/mL}$ ]), RU42698 ( $IC_{50}$  of  $26 \mu\text{M}$  [ $12 \mu\text{g/mL}$ ]), and RU42848 ( $IC_{50}$  of  $>3 \mu\text{M}$  [ $>1 \mu\text{g/mL}$ ]) caused a concentration-related inhibition of potassium selective  $I_{Kr}$  (tail) current.
- The  $IC_{50}$  concentrations of mifepristone and RU42848 could not be determined due to solubility limitations.

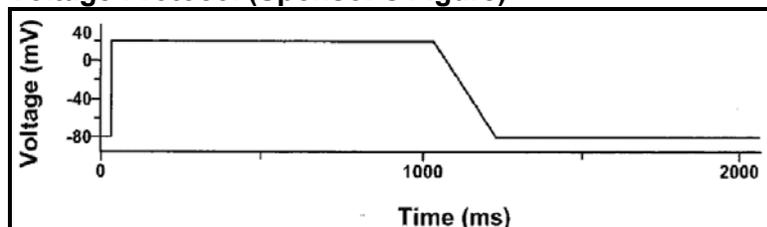
### Reviewer's Comments

The  $IC_{50}$  values established for mifepristone ( $>4 \mu\text{g/mL}$ ;  $\sim 1\text{X}$  of the clinical  $C_{\text{max}}$  of  $3 \mu\text{g/mL}$ ), RU42633 ( $6 \mu\text{g/mL}$ ;  $\sim 4\text{X}$  of the clinical  $C_{\text{max}}$  of  $1.7 \mu\text{g/mL}$ ), RU42698 ( $12 \mu\text{g/mL}$ ;  $\sim 17\text{X}$  of the clinical  $C_{\text{max}}$  of  $0.7 \mu\text{g/mL}$ ), and RU42848 ( $>1 \mu\text{g/mL}$ ;  $\sim 1\text{X}$  of the clinical  $C_{\text{max}}$  of  $1.3 \mu\text{g/mL}$ ) each exceed the peak plasma concentrations at the MRHD of  $1200 \text{ mg/day}$  in healthy volunteers.

### Methods

HEK293 cells were cotransfected with the hERG potassium channel cDNA and G418-resistant gene. Cells stably expressing hERG were held at  $-80 \text{ mV}$ . Onset and steady state inhibition of hERG potassium current in the presence of test article were measured using a pulse pattern with fixed amplitudes (depolarizing prepulse,  $+20 \text{ mV}$ ; repolarizing test ramp,  $+20 \text{ mV}$  to  $-80 \text{ mV}$  at  $-0.5 \text{ V/s}$ ) repeated at 5 second intervals from the holding potential of  $-80 \text{ mV}$ . Each recording ended with a final application of a supramaximal concentration of the reference substance (E-4031,  $500 \text{ nM}$ ) to assess the contribution of endogenous currents. The remaining uninhibited current was subtracted off-line digitally from the data to determine the potency of the test substance for hERG inhibition. One or more test article concentrations were applied sequentially (without washout between test article concentrations) in ascending order, to each cell ( $n \geq 3$ ). Peak current were measured during the test ramp. A steady state was maintained for at least 20 seconds before applying test article or positive control. Peak current were measured until a new steady state was achieved or 12 minutes of exposure time have elapsed. Terfenadine ( $60 \text{ nM}$ ) was used as the positive control; applied to at least two cells ( $n \geq 2$ ). Vehicle control solution was applied to at least four cells ( $n \geq 3$ ) for a duration at least as long as longest application of test article in the study ( $\leq 12$  minutes). The highest concentration evaluated for each test article was the highest soluble concentration of that test article in the assay vehicle; RU42633 ( $3\text{-}30 \mu\text{M}$ ;  $1\text{-}13 \mu\text{g/mL}$ ), RU42698 ( $1\text{-}30 \mu\text{M}$ ;  $0.5\text{-}13 \mu\text{g/mL}$ ), and RU42848 ( $1\text{-}3 \mu\text{M}$ ;  $0.4\text{-}1 \mu\text{g/mL}$ ).

### Voltage Protocol (Sponsor's Figure)



## Results

Mifepristone and its metabolites (RU42633, RU42698, and RU42848) caused a concentration-related inhibition of potassium selective  $I_{Kr}$  (tail) current. The  $IC_{50}$  concentrations for hERG inhibitory effect of RU42633 and RU42698 were 15  $\mu$ M and 26  $\mu$ M, respectively. Due to the solubility limitations, the  $IC_{50}$  concentrations of mifepristone and RU42848 could not be determined, but were estimated to be greater than 10  $\mu$ M and 3  $\mu$ M, respectively. Terfenadine (60 nM) produced 76% inhibition of hERG channel mediated potassium currents confirming the sensitivity of the test system to hERG inhibition.

The stability, homogeneity and concentration were verified by HPLC for all formulations.

hERG Inhibition							
Test Article	Percent Inhibition of hERG Current (%)						$IC_{50}$
	0 $\mu$ M	1 $\mu$ M	3 $\mu$ M	6 $\mu$ M	10 $\mu$ M	30 $\mu$ M	
Mifepristone	0.7	--	13	22	32	--	>10
RU42633	0.5		13	--	35	73	15
RU42698	1	10	19	--	35	52	26
RU42848	0.5	3	9	--	--	--	>3

Value is statistically different from vehicle alone.

## 5 Pharmacokinetics/ADME/Toxicokinetics

### 5.1 PK/ADME

Single and multiple-dose pharmacokinetic (PK) data have been obtained in mice, rats, dogs, and monkeys in toxicology studies conducted by the sponsor. The sponsor also conducted six *in vitro* studies to further assess the pharmacokinetics and drug-drug interactions. Additional PK/ADME data was obtained from the published literature.

#### Methods of Analysis

Plasma concentration of mifepristone, RU42633, RU42698, and RU42848: Reverse phase LC/MS/MS method with a lower limit of quantification of 10 ng/mL in mouse, rat, dog, and monkey.

#### Absorption

In single dose studies in humans (1.3-3.5 mg/kg), monkeys (3 mg/kg), and rats (5 mg/kg), mifepristone was readily absorbed (Deraedt et al., 1985). While the apparent initial volume of distribution was relatively high the rat (equivalent to body weight) and monkey (~2X body weight), it accounted for only ~10% of the body weight of humans. The rate of clearance was significantly less in humans (23 mL/hr/kg) compared to rats and monkeys (1.5-6 L/hr/kg). Reduced bioavailability across species is attributed to metabolism in the splanchnic circulation.

**Single Dose PK of Mifepristone in Rats and Monkeys (Deraedt et al., 1985)**

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In addition, a single-dose pharmacokinetic study in dogs (Study PK-005) in which mifepristone was administered orally (100, 200, 400, and 800 mg/kg) and subcutaneously (402 mg/kg) established saturation of absorption at  $\geq 400$  mg. Subcutaneous absorption was slower and led to much lower plasma concentrations than for the corresponding oral dose.

**Distribution**

The sponsor did not conduct an *in vivo* distribution study. However, several published studies demonstrated that the drug is widely distributed following oral exposure.

A published study demonstrated radio-labeled mifepristone is rapidly and widely distributed in the rat following oral administration (5 mg/kg) (Deraedt et al., 1985). At 0.5 hours postdose, concentrations in most organs/tissues exceeded that of the plasma in male rats. Levels were highest in the stomach, gastrointestinal tract (stomach and duodenum), perirenal fat, adrenal gland, pancreas, subcutaneous fat, and kidney. Radioactivity was detected in the brain (although at relatively low concentrations) demonstrating the ability of the drug to cross the blood brain barrier. Twenty four hours postdose, radioactivity concentrations were significantly lower in all tissues (~15-140X lower) except in erythrocytes (~2X higher), which was attributed to the covalent binding to the protein part of hemoglobin. Radioactivity levels in the liver, duodenum, erythrocytes, kidney, and thyroid exceeded plasma levels at 24 hours postdose, although each accounted for ~1-10% of the dose. Distribution in females administered the same dose was similar although fewer organs/tissues were assessed.

**Radioactivity Distribution in the Male Rat at 0.5 Hours Postdose (Deraedt et al., 1985)**  
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**Radioactivity Distribution in the Male Rat at 24 Hours Postdose (Deraedt et al., 1985)**  
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**Radioactivity Distribution in the Female Rat at 0.5 Hours Postdose (Deraedt et al.,**

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**Radioactivity Distribution in the Female Rat at 24 Hours Postdose (Deraedt et al.,**

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A subsequent autoradiographic study in female rats at 0.25, 1, and 6 hours postdose (5 mg/kg; IV) demonstrated a high rate of extravascular diffusion by the contrast between blood radioactivity in the cardiac cavity and heart radioactivity (Deraedt et al., 1985). The study also identified selective areas of labeling in the brain (hippocampus, cortex, pineal gland, and hypophysis) and adrenal gland (cortex).

A later study by Heikinheimo and colleagues determined the distribution of mifepristone and its demethylated metabolites (RU42633 and RU42848) in serum, brain, muscle, and adipose tissue of lean and obese Zucker rats administered an oral dose of 10 mg/kg twice daily (20 mg/kg/day) for 3.5 days (Heikinheimo et al., 1994). All animals exhibited measurable amounts of mifepristone and its demethylated metabolites in the brain, with an average concentration of 24-28% of the serum level. Interestingly, the brain tissue concentrations were higher in obese mice compared to the lean mice. Concentrations of mifepristone (~40X ↑) and the metabolites (~7X ↑) were notably higher in adipose tissue than in serum, while concentrations in muscle tissue and serum were comparable. The depot in adipose tissue suggests possible redistribution from the fat compartment resulting in prolonged serum concentrations. Overall, the distribution of the demethylated metabolites (RU42633 and RU42848) was comparable with that of the parent compound.

Mifepristone and its metabolite RU42633 are transported across the placenta (Hill et al., 1991). In monkeys, there is some evidence that placental transfer diminishes later in gestation (Wolf et al., 1988)

### Plasma Protein Binding

In human serum, mifepristone is highly bound to alpha1-acid glycoprotein (AAG) and approaches saturation at doses of 100 mg or more at a plasma concentration of 2.5  $\mu\text{M}$  (1074 ng/mL) (Heikinheimo et al., 1987b). Mifepristone is also extensively bound to albumin (Kawai et al., 1987).

An *in vitro* study conducted by the sponsor established the protein binding of mifepristone in rat, monkey, and human plasma (Study PK-001). As assessed by ultracentrifugation and equilibrium dialysis, mifepristone (10  $\mu\text{M}$ ; 4.3 ng/mL) was highly protein bound ( $\geq 94\%$ ) in all species, reaching equilibration after 24 hours.

### Plasma Protein Binding of Mifepristone (Sponsor's Table)

Species	Ultracentrifugation	Equilibrium Dialysis		
		4 hour	24 hour	36 hour
Rat	97.7% (0.4)	99.4% (0.1)	98.1% (0.5)	98.2% (0.2)
Monkey	93.6% (0.8)	98.8% (0.3)	96.9% (0.6)	98.1% (0.3)
Human	98.7% (0.1)	99.6% (0.1)	99.2% (0.1)	99.6% (0.03)

Using pooled human plasma, the sponsor also conducted an *in vitro* evaluation of the binding of mifepristone and its three main metabolites (RU42633, RU42698, and RU42848) to human plasma proteins (AAG [69 g/dL] and albumin [3.8 g/dL]) at concentrations (0.2-10  $\mu\text{g/mL}$ ) exceeding peak plasma levels at the MRHD by approximately 3- to 14-fold (Study PK-002). Binding was approximately 99% for mifepristone, 99% for RU42633, 98% for RU42698, and 96% for RU42848 and was only slightly concentration-dependent over the range tested. The study did not assess the binding of mifepristone in the presence of its metabolites and *vice versa*.

### Metabolism

Mifepristone is metabolized through a two-step demethylation of the 11 $\beta$ -dimethylaminophenyl ring and hydroxylation of the 17- propynyl side chain to produce the mono-demethylated (RU42633), di-demethylated (RU42848), and hydroxylated (RU42698) metabolites (Jang et al., 1996; Agarwai, 1996). These three metabolites, which are pharmacologically active (Deraedt et al., 1985), subsequently undergo further hydroxylation or acetylation. A total of six metabolites have been identified in S9 protein fractions from rat, monkey, and human hepatocytes, with the rat demonstrating the most extensive metabolism (Wu et al., 1999). The biological activity of M4, M5, and M6 has not been established, although each was found to be less than 10 percent of total drug-related exposure.

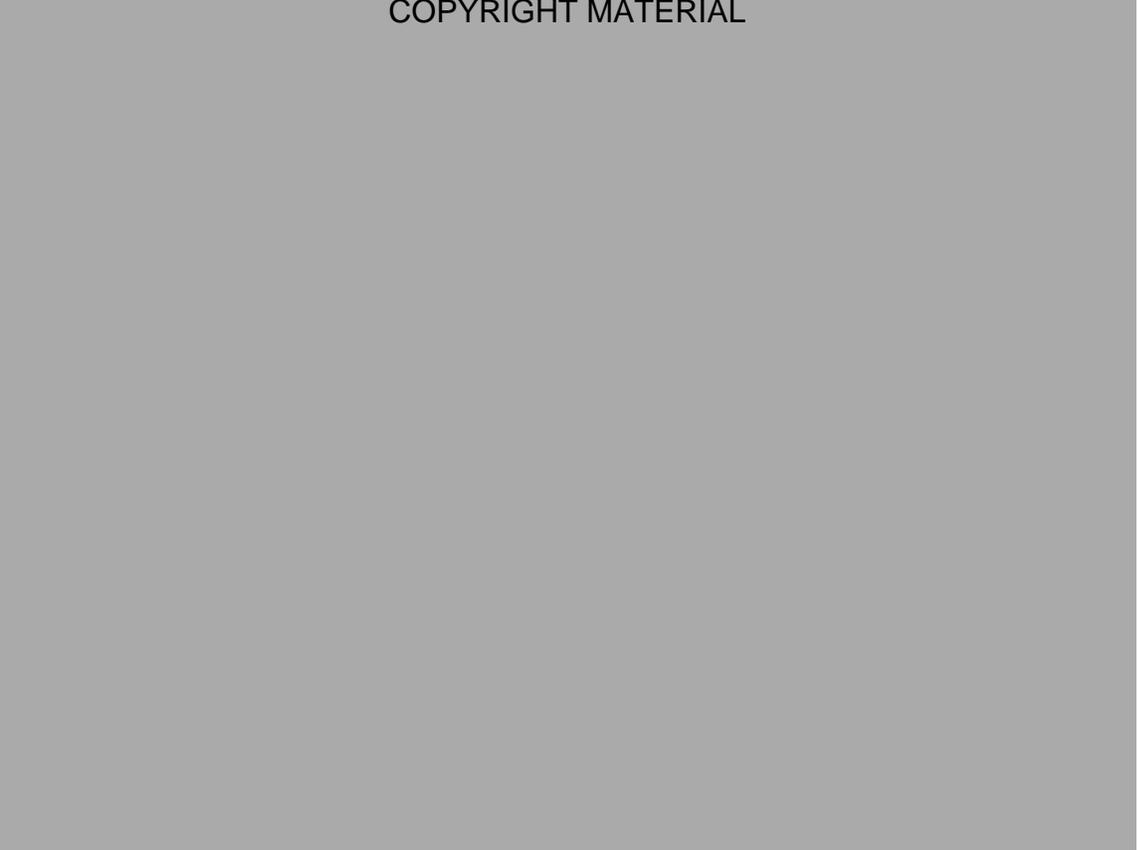
**In Vitro Metabolism of Mifepristone in Rat, Monkey and Human Hepatocytes at**

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**In Vitro Metabolism of Mifepristone in the Rat, Monkey, and Human (Wu et al., 1999)**

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The sponsor demonstrated that the three major pharmacologically active metabolites (RU42633, RU42848, and RU42698) in humans were present in the mouse, rat, dog, and monkey.

CYP3A4 was identified as the enzyme primarily responsible for mifepristone demethylation and hydroxylation in human liver microsomes (Jang et al., 1996). In a rat hepatoma cell line (Fao cells), CYP2B and CYP2C were also found to contribute markedly to the demethylation process of the molecule, although CYP3A is not present in this cell line (Chasserot-Golaz and Beck, 1992).

**Excretion**

In the rat, monkey, and human, excretion is mainly fecal with less than 10% of the dose recovered in the urine (Deraedt et al., 1985).

**Drug-Drug Interaction**CYP Inhibition

Mifepristone is a potent, irreversible, mechanism-based inactivator of CYP3A4 ( $K_i=4.7 \mu\text{M}$  [ $2 \mu\text{g/mL}$ ]) via apoprotein modification (He et al., 1999). Inactivation is time- and concentration-dependent, and requires the metabolism of mifepristone. Mifepristone ( $10\text{-}100 \mu\text{M}$ ;  $\sim 4.3\text{-}43 \mu\text{g/mL}$ ) also causes irreversible inhibition of CYP3A2 and competitive inhibition of CYP1A, CYP2B, and CYP2D6 activity.

**Inhibition of the activities of CYP 1A, 2B, 2D6, 2E1, and 3A by Mifepristone (He et al., 1999)**

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**CYP3A4 Inhibition (He et al., 1999; Zhou, 2008)**

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The sponsor conducted two *in vitro* studies to determine the inhibition potential ( $K_i$  and  $IC_{50}$ ) of mifepristone and its three main metabolites using human liver microsomes (Study PK-003 and Study PK-004) to further evaluate the inhibitory effect of mifepristone on various CYP450 enzymes.

The CYP450 inhibition by mifepristone and its metabolites was determined in human liver microsomes using marker substrates for nine CYP450 isoforms (Study PK-004). Metabolism of the marker substrates was assayed using LC/MS/MS. "Medium" inhibitory effects ( $IC_{50}$ ,  $1\text{-}10 \mu\text{M}$ ) of mifepristone and/or its metabolites were observed for five of the

nine isoforms: CYP2A6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 (the latter using both midazolam and testosterone as substrates).

**IC<sub>50</sub> Determination for Mifepristone and its Three Active Metabolites in CYP450 in Human Liver Microsomes Incubated using Recombinant CYP450 Isoforms (Sponsor's Table)**

Isoform	Probe Substrate	IC <sub>50</sub> (μM)				Control Inhibitor	IC <sub>50</sub> (μM)
		Mifepristone	RU 42633	RU 42698	RU 42848		
1A2	Phenacetin	NI	NI	> 50	NI	Furafylline	6.5
2A6	Coumarin	> 50	> 50	8.5	>50	Tranlycypromine	1.6
2B6	Bupropion	NI	NI	> 10	>50	Tranlycypromine	5.8
2C8	Paclitaxel	8.6	3.5	> 10	6.7	Quercetin	1.9
2C9	Diclofenac	> 10	> 10	3.0	>10	Sulfaphenazole	0.24
2C19	S-Mephenytoin	> 10	NI	8.5	>50	n-Benzylirvanol	5.8
2D6	Dextromethorphan	> 10	> 50	> 10	>10	Quinidine	0.082
2E1	Chlorzoxazone	NI	NI	NI	>50	Methylpyrazole	0.82
3A4	Midazolam	9.3	8.6	8.7	>10	Ketoconazole	0.013
3A4	Nifedipine	> 10	> 10	> 50	>10	Ketoconazole	0.11
3A4	Testosterone	> 10	8.1	> 10	>10	Ketoconazole	0.12

Legend	
Shade	Inhibition Potential
	Low (IC <sub>50</sub> >10 μM)
	Medium (IC <sub>50</sub> 1 - 10 μM)
	High (IC <sub>50</sub> <1 μM)

NI = No Inhibition

The sponsor then determined Ki values of mifepristone and/or one or more of its three active metabolites in human liver microsomes for inhibition of CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 with IC<sub>50</sub> values were less than 10 μM (i.e., medium inhibition potential) (Study PK-003). Using the industry-standard scale to define the likelihood of a drug-drug interaction (remote, 1/Ki < 0.1; possible, 0.1 < 1/Ki < 1; likely, 1/Ki > 1), the sponsor determined that a "likely" possibility of a drug-drug interaction was demonstrated for RU42633 with CYP2C8 substrates and for RU42698 with CYP2C9 substrates. All other isoforms/inhibitor combinations yielded "possible" interactions with exception of RU 42698, which showed a "remote" possibility of interaction with CYP3A4 substrates.

#### CYP Induction

*In vitro* and *in vivo* studies have also shown that mifepristone is an effective inducer of hepatic CYP3A. *In vitro* mifepristone (10<sup>-5</sup> M [4.3 ng/mL]; 2 days) induced CYP3A mRNA and protein in cultured rat (CYP3A1/2) and rabbit (CYP3A6) hepatocytes (Kocarek et al., 1995). Mifepristone (10<sup>-5</sup> M; 4 days) also induced a 3-fold increase in CYP3A mRNA levels in human hepatocytes relative to untreated controls. *In vivo* mifepristone increased hepatic levels of CYP3A as well as CYP3A-mediated enzyme activity (5X ↑) in female rats administered 50 mg/kg (IP) for four days. In addition, competitive RT-PCR studies showed that mifepristone increased hepatic microsomal and mRNA concentrations of CYP3A1, CYP3A18, and CYP3A23 mRNA in female rats administered 25 mg/kg twice daily (IP) for 2 days (Cheesman and Reilly, 1998)

In addition to CYP3A, mifepristone was shown to induce CYP2B. In C57BL/6NCrj mice, mifepristone (10 mg/kg; 3 days; SC) induced the expression of CYP2B10 mRNA in the female liver, although not in males or in the kidneys of either sex (Jarukamjorn et al., 2001). The same study also found that mifepristone (10<sup>-5</sup> M) induced hepatic CYP2B

mRNA expression specifically in females (more than 3-fold induction). A subsequent study in rat liver slices found that mifepristone (10-30  $\mu\text{M}$ ; 4300-12900 ng/mL) caused an elevation of CYP2B1/2 mRNA expression ( $\sim 15\text{-}20\text{X}$   $\uparrow$ ) and an elevation of CYP3A1 mRNA ( $\sim 15\text{-}30\text{X}$   $\uparrow$ ) compared to control values using real-time quantitative RT-PCR (Cui et al., 2005).

### Transporters

Although mifepristone is not a substrate of the transporter P-glycoprotein (P-gp), an *in vitro* study reported in the literature utilizing Madin-Darby canine kidney (MDCK) cells demonstrated that mifepristone significantly inhibited the renal tubular secretion of digoxin, suggesting that mifepristone is an inhibitor of P-gp (Woodland et al., 2003).

The sponsor conducted an *in vitro* transport interaction study of mifepristone with human efflux and uptake transporters (Study C-PK-006). Vesicular transport assays were used to investigate the interaction of the compound mifepristone with the human MDR1, MRP1, MRP2, MRP3, BCRP and BSEP transporters, and uptake transport assays were applied to study the effect of mifepristone on the NTCP, OATP1B1, OATP1B3, OATP2B1, OCT1 and OAT1 transporters. Mifepristone effectively inhibited substrate transport by the transporters MDR1 (IC<sub>50</sub>  $\sim 2$   $\mu\text{M}$  [0.8  $\mu\text{g}/\text{mL}$ ]), BCRP (IC<sub>50</sub>  $\sim 6$   $\mu\text{M}$  [2.4  $\mu\text{g}/\text{mL}$ ]), and BSEP (IC<sub>50</sub>  $\sim 3$   $\mu\text{M}$  [1.3  $\mu\text{g}/\text{mL}$ ]) at clinically relevant concentrations (C<sub>max</sub>=3.1  $\mu\text{g}/\text{mL}$ ; 1200 mg/day). Mifepristone also effectively inhibited substrate transport by the uptake transporters OAT1B1 (IC<sub>50</sub>  $\sim 9$   $\mu\text{M}$  [3.9  $\mu\text{g}/\text{mL}$ ]), OAT1B3 (IC<sub>50</sub>  $\sim 1$   $\mu\text{M}$  [0.4  $\mu\text{g}/\text{mL}$ ]) and OATP2B1 (IC<sub>50</sub>  $\sim 4$   $\mu\text{M}$  [1.9  $\mu\text{g}/\text{mL}$ ]).

### **Inhibitory Effects of Mifepristone on Transporters (Sponsor's Table)**

Assay	Transporter	Reporter Substrate	Reference Inhibitor	IC <sub>50</sub> ( $\mu\text{M}$ ) / Efficacy (%)
Vesicular Transport	MDR1	NMQ	Verapamil	1.8/100
	MRP1	LTC4	MK571	No Interaction
	MRP2	E <sub>2</sub> 17 $\beta$ G	Benzbromarone	No Interaction
	MRP3	E <sub>2</sub> 17 $\beta$ G	Benzbromarone	No Interaction
	BCRP	Estrone-3-Sulfate	K0143	5.6/87
	BSEP	Taurocholate	Cyclosporin A	3.1/98
Uptake	NTCP	Taurocholate	TCDC	70/68
	OATP1B1	Estrone-3-Sulfate	Cerivastatin	9.1/90
	OATP1B3	Fluo-3	fluvastatin	1.0/100
	OATP2B1	Estrone-3-Sulfate	fluvastatin	4.3/100
	OCT1	PAH	benzbromarone	67/58
	OAT1	TEA	verapamil	-/20

Key to abbreviations:

E<sub>2</sub>17 $\beta$ G = Estradiol-17- $\beta$ -glucuronide

LTC4 = Leukotriene C4

NMQ = N-methyl-quinidine

PAH = p-aminohippuric acid

TCDC = Taurocheno-deoxycholate

TEA = tetraethylammonium chloride

## **5.2 Toxicokinetics**

Single- and multiple-dose toxicokinetic data have been obtained in toxicity studies in mice, rats, dogs, and monkeys. In all species, mifepristone was metabolized into the three major, active metabolites RU42633, RU42698, and RU42848 identified in humans. In the chronic and subchronic studies, exposure (parent and 3 active metabolites) in all species did not exceed clinical exposure ( $\leq 1\text{X}$  MRHD of 1200 mg/day) due to the toxicity of the drug.

Although exposure increased with dose, exposure at the higher doses was generally less than dose proportional.

#### Mice

The toxicokinetics of mifepristone and its three major metabolites were established on Day 1 and Week 26 in the 104-week oral carcinogenicity study. Overall, RU42848 exposure slightly exceeded that of mifepristone, except at the highest dose in females. Systemic exposure to the parent and the three main metabolites changed with repeat dosing. In males and females, mifepristone exposures (AUC and C<sub>max</sub>) at Week 26 were generally lower or the same as those on Day 1. RU42633 and RU42698 exposures generally decreased with repeat dosing, while RU42848 exposures generally increased or remained the same.

#### Rats

The toxicokinetics of mifepristone and its three main metabolites were established on Day 1 and Week 26 in the 104-week oral carcinogenicity study. Metabolism was generally rapid with the detection of metabolite plasma concentrations within 1-2 hours of mifepristone administration. Although, peak plasma concentrations of RU42698 and RU42848 occurred 4-12 hours postdose at the high dose. Systemic exposure (C<sub>max</sub> and AUC<sub>0-24</sub>) increased with dose for all four analytes. RU42848 systemic exposure was highest in both sexes across all dose groups. With repeat dosing, exposure (AUC and C<sub>max</sub>) increased in males dosed at ≤25 mg/kg and females dosed at 5 mg/kg. However, changes in exposure of the four analytes following repeat dosing were variable at higher doses (125 mg/kg [males]; ≥25 mg/kg [females]) likely due to the complex pharmacokinetics of mifepristone. Overall, exposures (AUC and C<sub>max</sub>) to mifepristone and its three metabolites were appreciably higher in female rats as compared to males following both single and multiple doses.

#### Dogs

Toxicokinetics were established on Day 1, Week 13, and Week 26 in a 12-month dog study. Following single and multiple dosing, plasma concentrations of the parent mifepristone were higher than those of the three individual metabolites (RU42633, RU42698, and RU42848). Across all dose groups, peak plasma concentration and the systemic exposure of mifepristone and its three main metabolites notably increased at Week 13 (compared to Week 1) suggesting possible drug accumulation. However, at Week 26, there was no further increase in C<sub>max</sub> or AUC. In general, there was a slight decrease in systemic exposure at Week 26 (compared to Week 13). There were no consistent differences between genders.

### Monkeys

In 28-day study, the toxicokinetics were established on Days 1, 14, and 28 in the monkey. Exposure to each of the three metabolites (RU42848, RU42633, and RU42698) was higher than mifepristone exposure, with RU42848 achieving the highest exposure. While RU42848 systemic exposure increased (AUC) with dose, the C<sub>max</sub> values appeared to be saturated at the mid dose of 15 mg/kg with single and repeat dosing. At mid and high dose ( $\geq 15$  mg/kg), there was a  $\geq 2$ -fold increase in RU42633, RU 42698, and mifepristone exposures (AUC and C<sub>max</sub>) of with repeat dosing. There were no significant differences between genders.

## **6 General Toxicology**

To support the proposed chronic indication for the treatment of Cushing's syndrome, the sponsor conducted several general toxicology studies in the mouse (up to 13 weeks), rat (up to 13 weeks), and dog (up to 12 months). A 28-day study in the monkey was conducted as well primarily to determine the pharmacokinetic profile of mifepristone.

### **6.2 Repeat-Dose Toxicity**

#### **4-Week Toxicity Study of C-1073 in Female Mice (T-003/50-006)**

0, 125, 250, 500, 750, 1000, and 1500 mg/kg (no TK data)

*Conducted to determine an MTD for female mice; MTD not established in 13-week study.*

NOAEL of 250 mg/kg; based on adverse liver effects at 500 mg/kg

Mortality at  $\geq 750$  mg/kg; associated with decreased activity, ataxia, tremors, hunched posture, and prostration

Treatment-related liver effects at  $\geq 500$  mg/kg

- Increased liver weight at  $\geq 500$  mg/kg
- Panlobular hypertrophy (centrilobular to periportal areas) at  $\geq 500$  mg/kg; increased acidophilic cytoplasm
- Individual hepatocyte necrosis in all mice that died prematurely at  $\geq 750$  mg/kg; shrunken acidophilic cytoplasm and pyknotic nuclei
- Increases in ALT (2-8X) and AST (2-8X) in individual animals at  $\geq 500$  mg/kg did not correlate with microscopic findings
- Increases in bilirubin (2-4X) at  $\geq 750$  mg/kg

Treatment-related kidney effects at  $\geq 500$  mg/kg

- Increased kidney weight at  $\geq 500$  mg/kg
- Tubular epithelial necrosis in all mice that died prematurely at  $\geq 750$  mg/kg
- Tubular regeneration at 500-1000 mg/kg; increased basophilia of nuclei and cytoplasm
- Increases in creatinine (4-6X) at  $\geq 750$  mg/kg

Increased thyroid weight at  $\geq 500$  mg/kg

Dose-related female reproductive organ changes

- Decreased uterine weight at  $\geq 250$  mg/kg
- Dilatation of uterine gland at  $\geq 500$  mg/kg
- Hyperplasia of squamous epithelium of the cervix and the vagina at  $\geq 500$  mg/kg
- Decreased ovary weight in mice that died prematurely ( $\geq 750$  mg/kg)

Atrophy of the thymus at  $\geq 500$  mg/kg; due to loss of cortical lymphocytes

Decrease in red cell mass at  $\geq 500$  mg/kg

**13-Week Oral Toxicity Study of C-1073 in Mice**

0, 12.5, 65, and 125 mg/kg (no TK data)

NOAEL of 65 mg/kg; based on decreased body weight gain and decreased thymus weight at 125 mg/kg

Decreased body weight and body weight gain at 125 mg/kg; males only

Increased liver weight at  $\geq 65$  mg/kg; no microscopic findings

Increased kidney weight at 125 mg/kg

Dose-related increased ceroid in adrenals at  $\geq 12.5$  mg/kg

Dose-related female reproductive organ changes at  $\geq 12.5$  mg/kg

- Decreased uterine weight with concomitant atrophy (minimal to mild)
- Uterine endometrial glandular dilation
- Increased (incidence and severity) diffuse squamous cell hyperplasia of cervical epithelium (diffuse thickening of the epithelial lining of the cervix) and vaginal epithelium (with increased keratinization)

Decreased thymus weight at 125 mg/kg and increased incidence of lymphoid necrosis in all dosed groups

**A 28-Day Toxicokinetic Study with C-1073 when Administered Once Daily by Oral Gavage to Sprague-Dawley Rats (T-004)**

5, 25, and 125 mg/kg (~0.02-0.05-X, 0.2-0.5X, and 1X MRHD of 1200 mg/day; AUC basis) *Mortality, clinical signs, body weights, gross pathology (HD only), and TK data.*

NOAEL of 25 mg/kg (26-62  $\mu\text{g}\cdot\text{h}/\text{mL}$ ; ~0.2-0.5X MRHD of 1200 mg/day; AUC basis); based on moribundity at 125 mg/kg (106-134  $\mu\text{g}\cdot\text{h}/\text{mL}$ ; ~1X MRHD of 1200 mg/day; AUC basis)

Mortality at 125 mg/kg; one moribund female (Day 9)

Dose-related decrease in body weight gain at  $\geq 25$  mg/kg; males only

Enlarged pituitary at 125 mg/kg

Thymus discoloration at 125 mg/kg

**13-Week Oral Gavage Toxicity Study of C-1073 in the Albino Rat (T-008)**

0, 1, 5, 25, and 125 mg/kg (~0.01-0.03-X, 0.1X, and 0.5X MRHD of 1200 mg/day; AUC basis)

NOAEL of 25 mg/kg (12-16  $\mu\text{g}\cdot\text{h}/\text{mL}$ ; ~0.1X MRHD of 1200 mg/day; AUC basis); based on liver effects ( $\uparrow$  weight and centrilobular hypertrophy) and decreased body weight gain at 125 mg/kg (48-57  $\mu\text{g}\cdot\text{h}/\text{mL}$ ; ~0.5X MRHD of 1200 mg/day; AUC basis)

Decreased body weight gain (12-14%  $\downarrow$ ) at 125 mg/kg

Increases in WBCs (total counts, lymphocytes, and monocytes) at  $\geq 25$  mg/kg; females only

Increased liver weight at  $\geq 25$  mg/kg and centrilobular hypertrophy at 125 mg/kg

Increased kidney weight at  $\geq 25$  mg/kg; females only

Increased thyroid weight at 125 mg/kg

Increased adrenal weight with concomitant enlargement at  $\geq 25$  mg/kg as well as cortical hypertrophy at all doses

Increased pituitary weight and hypertrophy of the pars distalis at  $\geq 5$  mg/kg; females only

Dose-related female reproductive organ changes at  $\geq 5$  mg/kg

- Ducts and/or alveoli ectasia in mammary glands (minimal-moderate)
- Follicular ovarian cysts

- Persistent estrus

Decreased prostate weight and inflammation at 125 mg/kg

#### 4-Week Oral Toxicity Study of C-1073 in Dogs (T-005/950-002)

0, 25, 100, and 400 mg/kg (~0.5X, 2-5X, and 2-10X MRHD of 1200 mg/day; AUC basis)

NOAEL of 25 mg/kg (66-78 µg·h/mL; ~0.5X MRHD of 1200 mg/day; AUC basis); based on moribundity at 100 mg/kg (196-593 µg·h/mL; ~2-5X MRHD of 1200 mg/day; AUC basis)

Mortality at ≥100 mg/kg due to moribundity

Decrease in body weight gain at ≥100 mg/kg but not dose-related

Increases in liver enzymes (e.g., GGT, ALP, ALT, AST), slight increases in creatinine, slight decreases in albumin, cholesterol, and glucose, and increases in liver weight (females only) at ≥100 mg/kg

Dose-related increased adrenal weight with concomitant diffuse cortical hyperplasia at ≥100 mg/kg

Increased pituitary weight at ≥100 mg/kg

Decreased ovary weights at 400 mg/kg; not examined microscopically

Decreased testes and epididymis weights at all doses; not examined microscopically

Decreased spleen and thymus weight at ≥100 mg/kg

Microscopic changes (e.g., acute inflammation, erosion, villous atrophy) in the gastrointestinal tract (stomach, small intestine, large intestine) at ≥100 mg/kg

#### 12-Month Oral Toxicity Study of C1073 in Dogs (T-012/950-004)

<b>Study #</b>	T-012/950-004
<b>Study Report Location</b>	Module 4; Volume 1.8-1.9
<b>Conducting Laboratory and Location</b>	(b) (4)
<b>Date of Study Initiation</b>	29 June 2004
<b>GLP Compliance</b>	Yes
<b>QA Statement</b>	Yes
<b>Drug, Lot #, and % Purity</b>	Mifepristone lot 70295AA002, 98.6% lot 70295AR001, 100.6% lot 70295AR002, 99.8%

#### Key Study Findings

- After 12-months of dosing, animals administered 10, 25, and 60/40 mg/kg mifepristone (~0.2X, 0.9X, and 1X MRHD of 1200 mg/day; AUC basis) had average exposures of 8-12, 37-51, and 40-69 µg·h/mL for the parent, 4-6, 23-28, 26-44 µg·h/mL of RU42633, 5-9, 20-28, and 20-31 µg·h/mL of RU42698, and 2-3, 14, 15-21 µg·h/mL of RU42848.
- Mortality occurred at 60 mg/kg due to moribundity (inappetance, decreased activity, dehydration, edema of the face, discolored gums, and hypothermia); dose reduced to 40 mg/kg at Week 17.

- Treatment-related findings in the liver included increased liver weight ( $\geq 10$  mg/kg), elevated ALT levels (60/40 mg/kg), and pigmentation ( $\geq 25$  mg/kg).
- In addition to a dose-related increase in heart weight at all doses, there was a slight QTc prolongation (6-8 msec) postdose in the high dose group (60/40 mg/kg) at Week 52.
- In males, the decrease testes and epididymides weight, degeneration/atrophy of seminiferous tubules, decreased numbers of mature spermatocytes within tubules of epididymides, and prostate atrophy with less secretory tubules/alveoli is pharmacodynamically-mediated. There were no treatment-related changes in serum testosterone or dihydroxytestosterone in males.
- Absent corpora lutea in the ovaries and uterine anestrus occurred at all doses in the majority of the animals.

### Reviewer's Comments

The NOAEL appears to be 25 mg/kg (93-121  $\mu\text{g}\cdot\text{h}/\text{mL}$ ;  $\sim 0.9\text{X}$  MRHD of 1200 mg/day; AUC basis) based on the significantly elevated ALT levels (11X  $\uparrow$ ) and QTc prolongation at 60/40 mg/kg (100-166  $\mu\text{g}\cdot\text{h}/\text{mL}$ ;  $\sim 1\text{X}$  MRHD of 1200 mg/day; AUC basis), although the dose of 25 mg/kg was associated with testicular/epididymal atrophy, degeneration/atrophy of the seminiferous tubules, increased heart and liver weight, liver pigmentation, and anestrus uteri. Furthermore, exposure at the 40 mg/kg dose (100-166  $\mu\text{g}\cdot\text{h}/\text{mL}$ ) was only marginally higher than at the 25 mg/kg dose (93-121  $\mu\text{g}\cdot\text{h}/\text{mL}$ ).

Exposure at the 60 mg/kg dose (295-394  $\mu\text{g}\cdot\text{h}/\text{mL}$ ) causing moribundity was approximately 3-fold higher than the estimated exposure at the MRHD of 1200 mg/day (122  $\mu\text{g}\cdot\text{h}/\text{mL}$ ). This is in accord with the 4-week study where exposure at the 100 mg/kg dose (196-593  $\mu\text{g}\cdot\text{h}/\text{mL}$ ) causing mortality/moribundity was approximately 2- to 5-fold higher than the estimated exposure at the MRHD of 1200 mg/day. Thus, assessing higher doses achieving exposures greater than the estimated clinical exposure at the MRHD was not feasible due to tolerability.

As pharmacokinetics in dogs and monkeys (1-month studies) established that higher exposure could be achieved in the dog, the dog was selected as the nonrodent species for the chronic toxicity study.

The liver appears to be a target organ of toxicity ( $\uparrow$  weight, hepatocellular pigment, and ALT) in the dog at clinically relevant doses. The treatment-related increase in hepatocellular pigment is possibly lipofuscin based on the description provided by the sponsor; the sponsor only used stains to identify iron (hemosiderin) and bile salts. However, the clinical relevance of this histopathological finding is unknown. The treatment-related increases in ALT levels were generally 2-fold higher than baseline values. However, 11-fold increases occurred in two high dose males, one of which was euthanized on Day 103 and found to have hepatocyte necrosis, centrilobular vacuolation, inflammation, pigmentation, and congestion in the liver. The other male with significantly elevated ALT levels only had increased pigmentation.

<b>Doses</b>	0, 10, 25, and 60/40* mg/kg *Dose reduced from 60 mg/kg to 40 mg/kg at Week 17
<b>Frequency of Dosing</b>	Daily
<b>Route of Administration</b>	Oral; gelatin capsule
<b>Species/Strain</b>	Dog/Beagle (b) (4)
<b>Number/Sex/Group</b>	4/sex/group
<b>Age</b>	5-6 months
<b>Weight</b>	Females: 6.63-9.03 kg Males: 7.76-10.62 kg
<b>Unique Study Design</b>	Approximately 1 gram portions of the left testis were analyzed for intra-testicular testosterone levels.
<b>Deviation from Study Protocol</b>	None

### Observations Times and Results

#### Mortality

*Twice daily.*

Two males dosed at 60 mg/kg were euthanized in extremis on Day 21 (#126) and Day 103 (#127). Animals exhibited thin appearance, decreased activity, dehydration, feces few or absent, edema of the face (dorsal cervical and thoracic region), discolored gums, and hypothermia.

Gross and microscopic findings in the liver (centribolular vacuolation, congestion [#127 only], individual hepatocyte necrosis [#127 only], and increased pigmentation [#127 only]), gastrointestinal tract (inflammation and ulcerations/erosion), bone marrow (necrosis and depletion; #127 only), thymus (small and lymphoid depletion), and body fat depletion (#126 only) indicate that the dose exceeded tolerability.

At Week 13, mifepristone systemic exposure (12052 ng/mL; 241672 ng·h/mL) of the one male dog euthanized in extremis on Day 103 was ~2X higher than the male and female dogs in the high dose group. There was no notable difference in systemic exposure to mifepristone on Day 1 between the animals.

#### Clinical Signs

*Weekly.*

During Week 3, one female dosed at 60 mg/kg exhibited decreased activity, thin appearance, and inappetance. Following the supplementation of food and fluids, the animal recovered and clinical observations subsided. *The high dose of 60 mg/kg required a reduction to 40 mg/kg at Week 17 due to tolerability issues.*

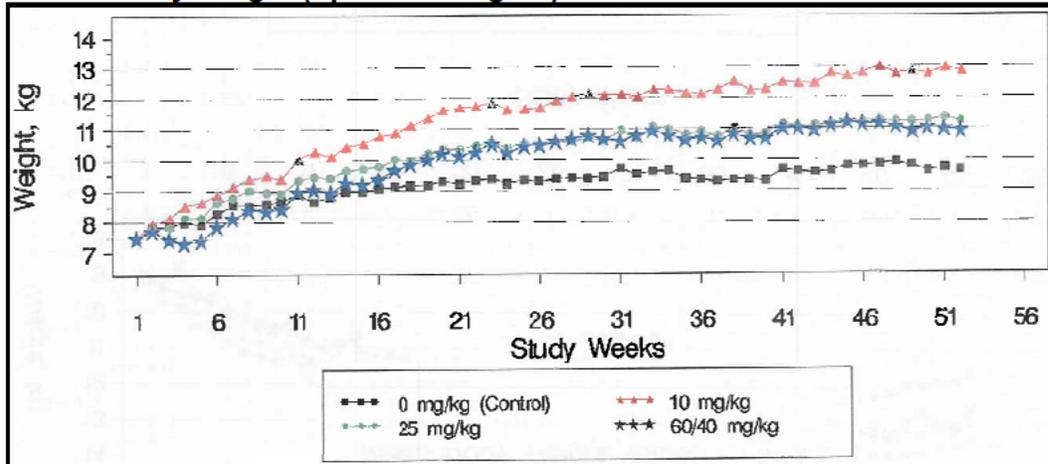
In females, there was a dose-related increase in lacrimation in females dosed at  $\geq 10$  mg/kg starting at Week 3. In addition, females dosed at 60/40 mg/kg also had enlarged vulva starting at Week 10.

**Body Weights**

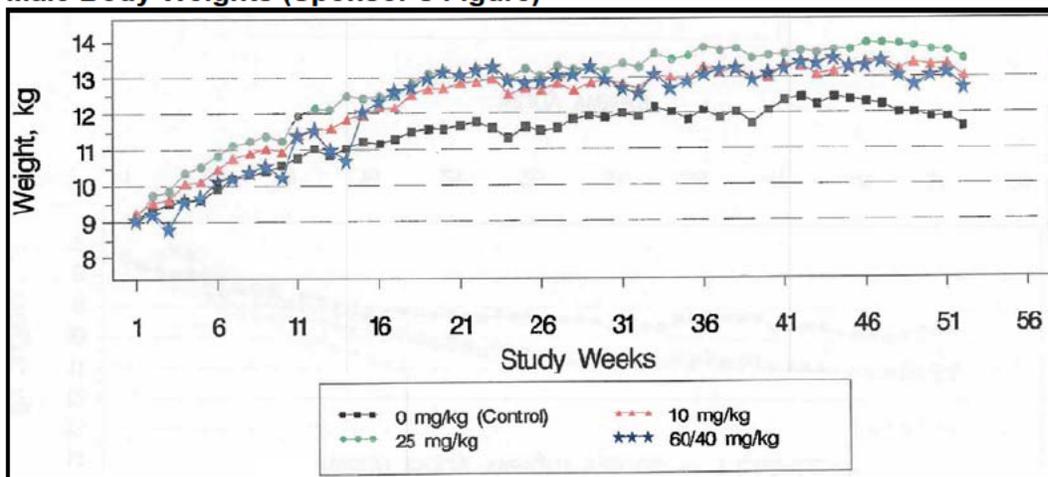
*Pretest and weekly during dosing.*

There was an increase in body weight in all treated groups (male and female) compared to controls. However, the increases were not appreciably dose-related.

**Female Body Weight (Sponsor's Figure)**



**Male Body Weights (Sponsor's Figure)**



Body Weight						
Dose (mg/kg)	Males			Females		
	Week 1 BW (g)	Week 52 BW (g)	% Difference*	Week 1 BW (g)	Week 52 BW (g)	% Difference*
0	9.07	11.60	--	7.46	9.67	--
10	9.26	13.02	12%	7.50	12.86	33%
25	9.10	13.49	16%	7.45	11.23	16%
60/40	9.06	12.69	9%	7.50	10.93	13%

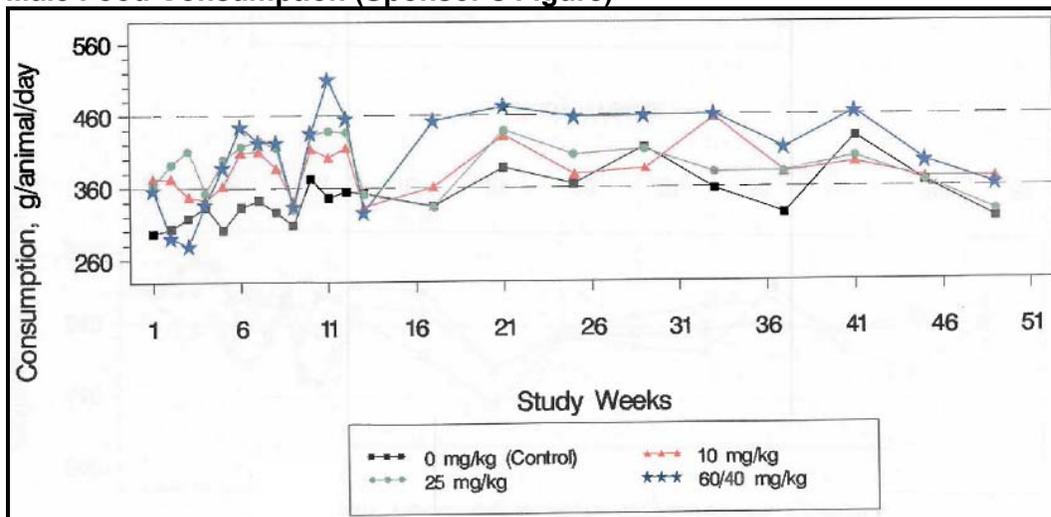
\* Percent difference from controls at Week 52

**Food Consumption**

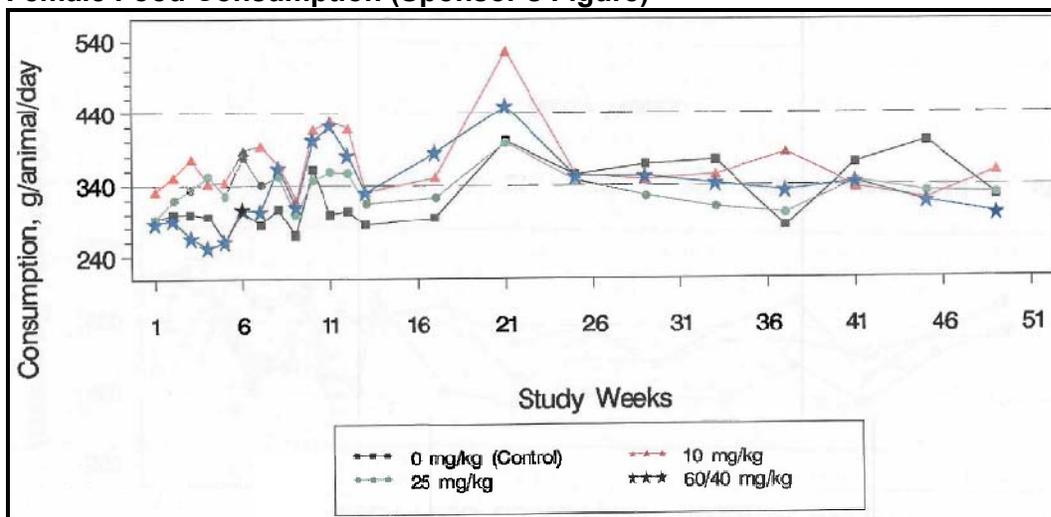
*Weekly for Weeks 1-13 and every 4 weeks thereafter.*

Overall, food consumption in all treated groups (males [11-18% ↑] and females [5-16% ↑]) was higher than controls for the duration of the study. The increase in food intake generally corresponded to the increase in body weight gain.

**Male Food Consumption (Sponsor's Figure)**



**Female Food Consumption (Sponsor's Figure)**



**Ophthalmoscopy**

*Pretest and Weeks 13, 26, 39, and 52.*

There were no test article-related ophthalmic findings.

**ECG**

Pretest and Week 52 (Day 358) at predose and ~1 hour postdose. RR, PR, and QT intervals, and QRS duration measured using Lead II (50 mm/sec). QT interval corrected (Fridericia).

There was a dose-related prolongation of the QT and QTc intervals in males and females dosed at  $\geq 25$  mg/kg at Week 52 compared to pretest values. A slight QTc prolongation (6-8 msec) postdose was observed only in the high dose group (60/40 mg/kg) relative to predose values at Week 52. There were no significant effects on heart rate, RR intervals, PR intervals or QRS duration.

**Male QT Interval (msec) (Sponsor's Table)**

Study Interval	0 mg/kg (Control)			10 mg/kg			25 mg/kg			60/40 mg/kg		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Pretest	175.35	2.604	4	173.75	5.422	4	178.20	5.448	4	175.30	7.495	2
Week 52 predose	180.70	6.734	4	184.30	12.313	4	194.20	11.583	4	186.20	18.102	2
Week 52 postdose	176.10	8.555	4	183.85	5.760	4	195.75 <sup>a</sup>	11.286	4	194.00	9.051	2

**Female QT Interval (msec) (Sponsor's Table)**

Study Interval	0 mg/kg (Control)			10 mg/kg			25 mg/kg			60/40 mg/kg		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Pretest	175.85	4.051	4	177.20	10.574	4	170.35	6.223	4	188.10	10.893	4
Week 52 predose	172.35	10.082	4	179.30	8.912	4	182.65	5.677	4	192.40 <sup>a</sup>	11.756	4
Week 52 postdose	177.50	9.640	4	179.50	6.206	4	183.50	8.245	4	198.50	24.596	4

**Male Corrected QT Interval (Fridericia; msec) (Sponsor's Table)**

Study Interval	0 mg/kg (Control)			10 mg/kg			25 mg/kg			60/40 mg/kg		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Pretest	232.80	10.524	4	239.50	8.017	4	241.15	4.352	4	232.80	11.031	2
Week 52 predose	224.23	12.691	4	233.40	4.033	4	246.15 <sup>a</sup>	12.212	4	251.30 <sup>b</sup>	7.778	2
Week 52 postdose	219.35	11.665	4	240.55	8.097	4	250.25 <sup>a</sup>	17.466	4	252.70 <sup>a</sup>	5.515	2

**Female Corrected QT Interval (Fridericia; msec) (Sponsor's Table)**

Study Interval	0 mg/kg (Control)			10 mg/kg			25 mg/kg			60/40 mg/kg		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Pretest	233.55	7.307	4	248.10 <sup>a</sup>	7.674	4	238.50	6.690	4	239.50	6.535	4
Week 52 predose	239.85	8.813	4	249.45	2.615	4	252.60 <sup>a</sup>	6.575	4	263.55 <sup>c</sup>	3.214	4
Week 52 postdose	245.65	6.894	4	251.95	7.459	4	257.85	13.248	4	270.40 <sup>b</sup>	5.899	4

**Hematology**

Pretest and Weeks 13 (Day 85), 26 (Day 181), 39 (Day 273), and 52 (Day 360); fasted overnight. Analysis of coagulation parameters at necropsy.

There were no significant test article-related hematological changes.

### Clinical Chemistry

*Pretest and Weeks 13 (Day 85), 26 (Day 181), 39 (Day 273), and 52 (Day 360); fasted overnight. Testosterone and dihydrotestosterone measured in males only except at Week 39 in which samples were analyzed in males and females.*

There was a decrease in cholesterol levels at 25 mg/kg (~1.5X ↓) and 60/40 mg/kg (~2X ↓) compared to pretest levels; the greatest decrease was on Day 85 (Week 12).

There was an increase in ALT levels in males (2-11X ↑) and females (2-3X ↑) dosed at 60/40 mg/kg compared to pretest levels. A large (11X) increase on Day 85 in males was due to two animals (60/40 mg/kg), one of which was euthanized on Day 103 and found to have hepatocyte necrosis, centrilobular vacuolation, inflammation, pigmentation, and congestion in the liver. The only histopathological finding in the other male with elevated ALT was increased hepatocellular pigmentation.

An increase in ALP levels in males dosed at 60/40 mg/kg on Day 85 was due to a 6X increase (compared to pretest levels) in the male euthanized on Day 103, which may be attributed to the liver findings (discussed above) as well as the inflammation and ulcerations (necrosis) in the stomach.

On the day the two males dosed at 60 mg/kg were euthanized in extremis (Day 21 and Day 103), there was a decrease in potassium, chloride, and phosphorus, as well as an increase in ALP, total bilirubin, AST, ALT (slight in animal euthanized on Day 21), and the A/G ratio.

### Male Clinical Chemistry Parameters (Sponsor's Table)

Endpoint	Interval of Study	0 mg/kg (Control)			10 mg/kg			25 mg/kg			60/40 mg/kg		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Alkaline Phosphatase U/L	Predose	114.5	29.94	4	126.8	9.43	4	130.5	35.91	4	115.8	30.31	4
	Day 85	80.0	18.18	4	75.3	3.77	4	78.0	26.75	4	376.0	423.08	3
	Day 181	41.5	7.33	4	49.3	4.99	4	60.8	21.09	4	97.0#	48.08	2
	Day 273	41.8	5.68	4	51.8	6.40	4	55.3	21.75	4	125.5#	64.35	2
	Day 360	36.3	1.26	4	49.8	17.27	4	59.5	23.46	4	83.0#	31.11	2
ALT U/L	Predose	31.8	3.77	4	28.5	4.93	4	29.8	1.89	4	25.5	8.19	4
	Day 85	34.5	5.45	4	36.8	11.50	4	44.5	9.15	4	285.3	359.53	3
	Day 181	37.3	7.97	4	45.8	26.87	4	56.3	18.14	4	70.0#	63.64	2
	Day 273	39.3	7.46	4	45.8	20.71	4	48.8	8.62	4	106.5#	99.70	2
	Day 360	34.8	14.86	4	59.5	26.21	4	54.8	8.22	4	52.0#	26.87	2
Cholesterol mg/dL	Predose	184.3	25.49	4	199.8	22.17	4	189.8	27.80	4	175.0	5.10	4
	Day 85	141.0	12.25	4	147.8	19.79	4	127.5	19.94	4	99.3 <sup>a</sup>	23.54	3
	Day 181	138.3	16.28	4	158.5	13.18	4	141.5	23.69	4	116.5#	3.54	2
	Day 273	145.8	15.50	4	160.8	20.19	4	136.8	22.35	4	117.5#	7.78	2
	Day 360	131.0	8.29	4	143.5	31.16	4	132.5	34.35	4	102.0#	0.00	2

**Female Clinical Chemistry Parameters (Sponsor's Table)**

Endpoint	Interval of Study	0 mg/kg (Control)			10 mg/kg			25 mg/kg			60/40 mg/kg		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Alkaline Phosphatase U/L	Predose	120.8	41.79	4	110.8	42.55	4	128.3	17.80	4	117.3	28.50	4
	Day 85	89.8	32.25	4	55.8	24.01	4	82.8	26.22	4	95.0	54.30	4
	Day 181	69.8	39.45	4	32.3	10.63	4	71.8	13.67	4	70.0	51.70	4
	Day 273	75.5	47.86	4	33.0	11.34	4	69.5	12.45	4	71.8	56.43	4
	Day 360	71.3	40.90	4	38.5	16.62	4	94.8	18.26	4	68.5	59.87	4
ALT U/L	Predose	29.3	3.40	4	24.3	6.65	4	29.3	4.57	4	29.3	10.05	4
	Day 85	31.3	9.60	4	31.0	8.12	4	42.5	15.26	4	64.0	45.20	4
	Day 181	26.3	6.50	4	27.3	1.89	4	78.3	67.71	4	57.8	20.01	4
	Day 273	35.5	19.71	4	43.5	26.49	4	53.5	15.61	4	99.0	76.44	4
	Day 360	49.3	41.50	4	62.5	60.52	4	127.5	109.06	4	71.8	31.27	4
Cholesterol mg/dL	Predose	180.3	41.22	4	146.0	9.42	4	174.0	39.12	4	151.3	6.02	4
	Day 85	154.0	16.10	4	114.5 <sup>b</sup>	8.54	4	117.8 <sup>b</sup>	14.45	4	99.0 <sup>b</sup>	14.99	4
	Day 181	181.8	48.78	4	124.8 <sup>a</sup>	15.09	4	130.5	15.02	4	100.0 <sup>b</sup>	18.25	3
	Day 273	181.8	32.98	4	128.8	10.24	4	127.5	11.96	4	111.5 <sup>a</sup>	18.38	4
	Day 360	184.5	72.63	4	112.3 <sup>a</sup>	8.81	4	119.3	10.69	4	101.8 <sup>a</sup>	15.44	4

There were no consistent treatment-related changes in testosterone or dihydroxytestosterone in males.

**Testosterone and Dihydroxytestosterone Levels (Sponsor's Table)**

Endpoint	Interval of Study	0 mg/kg (Control)			10 mg/kg			25 mg/kg			60/40 mg/kg		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Testosterone ng/dL	Predose	31.3	54.50	4	4.0	0.00	4	9.8	11.50	4	27.8	47.50	4
	Day 85	230.8	99.00	4	34.5 <sup>b</sup>	31.67	4	71.3 <sup>a</sup>	45.73	4	100.0	86.06	3
	Day 181	203.0	108.01	4	36.5	42.54	4	42.8	28.43	4	75.5#	20.51	2
	Day 273	40.5	36.23	4	18.3	16.70	4	58.3	77.56	4	70.0#	11.31	2
	Day 360	153.5	160.77	4	106.3	82.25	4	82.0	40.84	4	202.0#	134.35	2
Dihydroxytestosterone ng/mL	Predose	0.060	0.0542	4	0.025	0.0191	4	0.048	0.0299	4	0.048	0.0377	4
	Day 85	0.185	0.0500	4	0.050 <sup>b</sup>	0.0163	4	0.073 <sup>b</sup>	0.0377	4	0.047 <sup>b</sup>	0.0462	3
	Day 181	0.150	0.0497	4	0.058 <sup>a</sup>	0.0275	4	0.045 <sup>a</sup>	0.0173	4	0.050#	0.0141	2
	Day 273	0.070	0.0424	4	0.028	0.0096	4	0.035	0.0191	4	0.055#	0.0212	2
	Day 360	0.133	0.1250	4	0.060	0.0183	4	0.058	0.0171	4	0.080#	0.0566	2

**Urinalysis**

*All surviving animals. Collected prior to the initiation of dosing, every 3 months during the study, and prior to termination. using steel pans placed under the cages for at least 16 hours. Volume, pH, specific gravity, protein, bilirubin, glucose, occult blood, ketones, urobilinogen, and microscopy of spun deposit.*

From Day 85, there was a test article-related increase in urinary volume at  $\geq 10$  mg/kg compared pretest values and controls.

**Male Urinary Volume (Sponsor's Table)**

Endpoint	Interval of Study	0 mg/kg (Control)			10 mg/kg			25 mg/kg			60/40 mg/kg		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Volume mL	Predose	83.75	15.478	4	67.50	38.622	4	107.50	51.235	4	78.75	11.087	4
	Day 85	61.50	56.560	4	117.50	32.787	4	165.00	71.063	4	180.00 <sup>a</sup>	32.787	3
	Day 181	78.00	53.907	4	135.00	83.666	4	90.00	83.865	4	105.00 <sup>#</sup>	21.213	2
	Day 273	25.00	14.720	4	137.50 <sup>b</sup>	37.528	4	105.00 <sup>a</sup>	67.454	4	187.50 <sup>#</sup>	187.383	2
	Day 360	45.75	45.043	4	183.75 <sup>a</sup>	120.580	4	127.50	32.787	4	137.50 <sup>#</sup>	144.957	2

**Female Urinary Volume (Sponsor's Table)**

Endpoint	Interval of Study	0 mg/kg (Control)			10 mg/kg			25 mg/kg			60/40 mg/kg		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Volume mL	Predose	105.00	34.881	4	77.50	23.979	4	96.25	23.229	4	107.50	16.583	4
	Day 85	76.25	37.500	4	98.75	31.192	4	221.25 <sup>b</sup>	108.733	4	270.00 <sup>b</sup>	176.871	4
	Day 181	115.00	27.080	4	125.00	18.708	4	216.25 <sup>a</sup>	88.259	4	365.00 <sup>b</sup>	165.731	4
	Day 273	77.50	15.000	4	131.25	86.156	4	190.00	115.253	4	232.50 <sup>a</sup>	106.497	4
	Day 360	125.00	90.416	3	81.25	22.867	4	147.50	56.199	4	156.25	43.851	4

**Gross Pathology**

*All animals at scheduled necropsies.*

There were no treatment-related findings in the animals sacrificed at the scheduled necropsy.

**Organ Weights**

*All surviving animals at scheduled necropsy; absolute weight and weight ratios (relative to brain and body weights). Refer to table below for specific organs weighted.*

Treatment-related organ weight changes (absolute and relative weights) in the liver, reproductive systems, and heart in both males and females. There were also changes in the spleen, thymus, and thyroid/parathyroid in the males.

**Heart**

There was a slight dose-related increase in heart weight (absolute and relative weight) in males (18-43% ↑; brain weight ratio) and females (31-49% ↑; brain weight ratio) at all doses. However, there were no microscopic findings in the heart associated with the increase in weight.

**Liver**

There was a dose-related increase in the liver weight (absolute and relative weight) of males (26-68% ↑; brain weight ratio) and females (47-58% ↑; brain weight ratio) at all doses (≥10 mg/kg). Corresponding liver effects included an increase in liver pigmentation was noted in animals dosed at ≥25 mg/kg and an increase in ALT occurred in animals dosed at 60/40 mg/kg.

Testes and Epididymides

There was a decrease in the absolute and relative weight of the testes (15-22% ↓; brain weight ratio) and epididymides (42-47% ↓; brain weight ratio) in males at all doses, although the decrease was not clearly dose-related. *Prostate was not weighed.*

Ovaries

In females dosed at 60/40 mg/kg, there was a slight decrease in the weight of the ovaries (26% ↓; brain weight ratio).

Thymus and Spleen

In males, the absolute and relative weights of the spleen (65% ↓; brain weight ratio) and thymus (42% ↓; brain weight ratio) decreased in animals dosed at 60/40 mg/kg. Microscopically, there was a dose-related increase in the severity of lymphoid depletion in the thymus of both males and females in all dose groups (≥10 mg/kg).

Thyroid/Parathyroid

There was also a dose-related increase in the weight of the thyroid/parathyroid in males dosed at 25 mg/kg (74% ↑; brain weight ratio) and 60/40 mg/kg and thyroid/parathyroid (97% ↑; brain weight ratio) compared to controls. There were no corresponding treatment-related microscopic findings.

Male Organ Weights (Brain Weight Ratio)				
Dose (mg/kg)	Heart	Liver	Testes	Epididymides
0	1.21	3.75	0.198	0.054
10	1.43	4.71	0.169	0.029
25	1.66	6.25	0.169	0.026
60/40	1.73	6.30	0.155	0.031

Shaded values indicate  $p < 0.05$  compared to control

Female Organ Weights (Brain Weight Ratio)			
Dose (mg/kg)	Heart	Liver	Ovaries
0	1.00	3.38	0.0124
10	1.32	4.98	0.0183
25	1.47	5.32	0.0117
60/40	1.49	5.33	0.0092

Shaded values indicate  $p < 0.05$  compared to control

**Histopathology**

*Control and 60/40 mg/kg groups: all organs listed in table below*  
*10 and 25 mg/kg groups: stomach (cardia, fundus, and pylorus), small intestine (duodenum, ileum, and jejunum), large intestine (cecum, colon, and rectum), liver, thymus, testes, epididymides, prostate, ovaries, and uterus.*

**Histopathology and Organ Weigh Inventory (Sponsor's Table)**

- Adrenal (2)*	- Larynx
- Aorta	- Liver [3 sections collected; 2 examined]*
- Bone with marrow [femur]	- Lung [2 sections examined]
- Bone with marrow [rib]	- Lymph node, mandibular [2 collected; 1 examined]
- Bone with marrow [sternum]	- Lymph node, mesenteric
- Bone marrow smear [2 collected] <sup>a</sup>	- Mammary gland [process females only]
- Brain [cerebrum, midbrain, cerebellum, medulla/pons]*	- Nictitans gland (2)
- Epididymis (2)*	- Pancreas
- Eye including optic nerve (2)	- Peyer's patch
- Gallbladder	- Pituitary*
- Gastrointestinal tract:	- Prostate
esophagus	- Salivary gland, mandibular [2 collected; 1 examined]
stomach [cardia, fundus, and pylorus]	- Salivary gland, sublingual [2 collected; 1 examined]
duodenum	- Sciatic nerve
jejunum	- Skeletal muscle, biceps femoris
ileum	- Skin
cecum	- Spinal cord [cervical, thoracic, and lumbar]
colon	- Spleen*
rectum	- Thymus*
- Gonads:	- Thyroid/parathyroid (2)*
ovary (2)*	- Tongue
testis (2)*	- Trachea
- Gross lesions	- Urinary bladder
- Heart*	- Uterus [both horns] with cervix
- Kidney (2)*	- Vagina

<sup>a</sup> Bone marrow smears were prepared at scheduled necropsies and held

\* Organ weighed

(2) Paired organ

Treatment-related findings were noted in the male and female reproductive systems, liver, and thymus.

The treatment-related effects noted in the prostate, testes, and epididymides were most likely due to the anti-androgenic effects.

Prostate

With the exception of the two males dosed at 60/40 mg/kg euthanized in extremis (Day 21 and Day 103), prostate atrophy (mild-severe) was noted in all treated males. The prostate glands were within normal limits in two high dose males euthanized in extremis suggesting that the atrophy develops after 14 weeks of treatment. Subgrossly, the sections of prostate from treated dogs were noticeable smaller with less glandular and tubular architecture than the controls. Microscopically, the prostates had significantly less secretory tubules/alveoli than the controls. *The weight of the prostate not was obtained.*

Testes/Seminiferous Tubules

In the testes, there was degeneration/atrophy of seminiferous tubules in all males dosed at  $\geq 25$  mg/kg that sacrificed following 12 months of treatment. Although the tubules contained numerous spermatogonia and spermatocytes, there were fewer developing spermatids within seminiferous tubules. There was a dose-related decrease in the absolute and relative weights of the testes at all doses.

Hemorrhage and necrosis was noted in the testes of the male (60/40 mg/kg) euthanized in extremis on Day 103. The sponsor attributed this to possible infarct.

#### Epididymides

There was a dose-related increase in the incidence and severity of oligospermia/germ cell debris (moderate-severe) in the epididymides of males dosed at  $\geq 25$  mg/kg. This was not observed in the two high dose males euthanized in extremis. This finding was characterized by significantly reduced numbers of mature spermatocytes within tubules of the epididymides compared to controls. The sponsor attributed the oligospermia/germ cell debris finding in the one male dosed 10 mg/kg to the spontaneous event of hypospermatogenesis of the testes (reduced proportions of germ cells, tubular shrinkage, and Sertoli cell prominence).

#### Uterus/Ovaries

The uterus of all treated females ( $\geq 10$  mg/kg) appeared to be in either an anestrus stage or remained in a prepuberty state that failed to mature. Corpora lutea were absent from the ovaries of all treated females except for one female dosed at 10 mg/kg, who had all stages of developing oocytes except mature tertiary follicles although the uterus if the animal was anestrus or in a state of prepuberty.

#### Liver

Increased hepatocellular pigmentation (minimal-mild) was observed in almost all males and females dosed at  $\geq 25$  mg/kg. The pigment, which was primarily within the hepatocytes and occasionally in a Kupffer cell, was characterized by intracytoplasmic round yellow brown granules (2-3 micrometer diameter). Special stains on liver sections of one female dosed at 60/40 mg/kg were negative for iron (hemosiderin) and bile salts. Given the color and location, it is possible that pigment is lipofuscin, a highly oxidized lipid material. Lipofuscin accumulates in aging tissue due to increased oxidative stress which represents an end product of oxidative degradation of lipids (Moorthy and Singhal, 2005; Mahesh et al., 2009).

#### Thymus

There was a dose-related increase in the severity of lymphoid depletion in the thymus in both males and females at all doses ( $\geq 10$  mg/kg). It is difficult to determine whether this is treatment-related or due to stress.

Lung

Although subacute lung inflammation was observed in two males in the control group (minimal), it was also observed in two males (minimal-mild) and two females (minimal) dosed at 60/40 mg/kg. The lungs of the animals dosed at 10 and 25 mg/kg were not examined.

Histopathology (Dosing)										
Tissue/ Finding	Severity	Male (mg/kg)					Female (mg/kg)			
		0	10	25	60/40		0	10	25	60/40
		4	4	4	2*	2	4	4	4	4
<b>Epididymides</b>										
Oligospermia/ germ cell debris, bilateral	Moderate		1	1						
	Severe			3		2				
<b>Testes</b>										
Degeneration/ atrophy, seminiferous tubules	Mild			3		2				
	Moderate			1						
Hemorrhage	Minimal				1					
Necrosis	Minimal				1					
<b>Prostate</b>										
Atrophy	Mild		1	1						
	Moderate		3	3		1				
	Severe					1				
<b>Lung</b>										
Inflammation, subacute	Minimal	2	NE	NE	1			NE	NE	2
	Mild		NE	NE	1			NE	NE	
<b>Liver</b>										
Increased hepatocellular pigment	Minimal			4	1				3	2
	Mild					2			1	2
<b>Thymus Gland</b>										
Lymphoid depletion	Minimal	1	1					2		
	Mild	3	2	2				1	1	4
	Moderate		1	2		2		1	2	3
	Severe				1				1	1

\* Euthanized in extremis

NE: not examined

**Toxicokinetics**

Day 1, Week 13 (Day 86), and Week 26 (Day 176): predose and at 1, 2, 4, 8, 12, and 24 hours postdose. Mifepristone and its three main metabolites RU42633, RU42698, and RU42848 were measured.

Mifepristone was metabolized to RU 42633, RU 42698 and RU 42848. Following single and multiple dosing, plasma concentrations of the parent mifepristone were higher than

those of the three individual metabolites (RU42633, RU42698, and RU42848). Overall, systemic exposure (C<sub>max</sub> and AUC<sub>0-24</sub>) to mifepristone and the three metabolites increased with dose. However, exposure was less than dose proportional.

Across all dose groups, peak plasma concentration and AUC of mifepristone and its 3 main metabolites notably increased at Week 13 (compared to Week 1) suggesting possible drug accumulation. However, at Week 26, there was no further increase in C<sub>max</sub> or AUC. In general, there was a slight decrease in systemic exposure at Week 26 (compared to Week 13). There were no consistent differences between genders.

#### Male TK Parameters (Sponsor's Table)

Analyte	Parameter	Dose Group (mg/kg/day)								
		10 (Group 2)			25 (Group 3)			60 or 40 <sup>b</sup> (Group 4)		
		Day 1	Week 13	Week 26	Day 1	Week 13	Week 26	Day 1	Week 13	Week 26
C-1073	C <sub>max</sub> , ng/mL	56.5	1029.3	671.6	615.8	3321.8	2209.5	2750.3	8429.2	2452.9
	T <sub>max</sub> <sup>a</sup> , h	4.0	1.5	12.0	2.0	1.0	1.5	7.0	2.0	6.5
	AUC(0-24), ng·h/mL	585.7	8359.2	7556.5	5930.4	50024.2	36603.7	20126.6	162391.8	40160.5
RU 42633	C <sub>max</sub> , ng/mL	30.7	461.1	281.8	336.0	1352.8	1183.5	1097.5	5382.4	1320.3
	T <sub>max</sub> <sup>a</sup> , h	4.0	1.5	12.0	13.0	1.5	1.5	14.0	2.0	6.0
	AUC(0-24), ng·h/mL	403.1	4862.8	3904.0	3477.2	26358.3	22747.7	12317.8	111361.4	25684.7
RU 42698	C <sub>max</sub> , ng/mL	41.3	494.8	391.1	408.0	1219.8	952.8	1317.6	3212.3	1077.3
	T <sub>max</sub> <sup>a</sup> , h	3.0	2.0	12.0	2.5	4.0	6.0	6.0	4.0	12.0
	AUC(0-24), ng·h/mL	420.4	5794.0	4895.1	4171.9	23900.0	19610.5	14256.8	65349.7	19611.7
RU 42848	C <sub>max</sub> , ng/mL	22.3	169.5	153.0	155.9	707.3	685.1	394.1	2779.7	765.6
	T <sub>max</sub> <sup>a</sup> , h	4.0	2.0	6.5	14.0	1.5	1.5	24.0	2.0	12.0
	AUC(0-24), ng·h/mL	337.7	2442.3	2323.8	2189.5	13781.5	14003.2	5550.9	54686.8	14953.6

<sup>a</sup> Expressed as median

<sup>b</sup> Dogs received 60 mg/kg/day for the first 16 weeks followed by 40 mg/kg/day thereafter due to toxicity

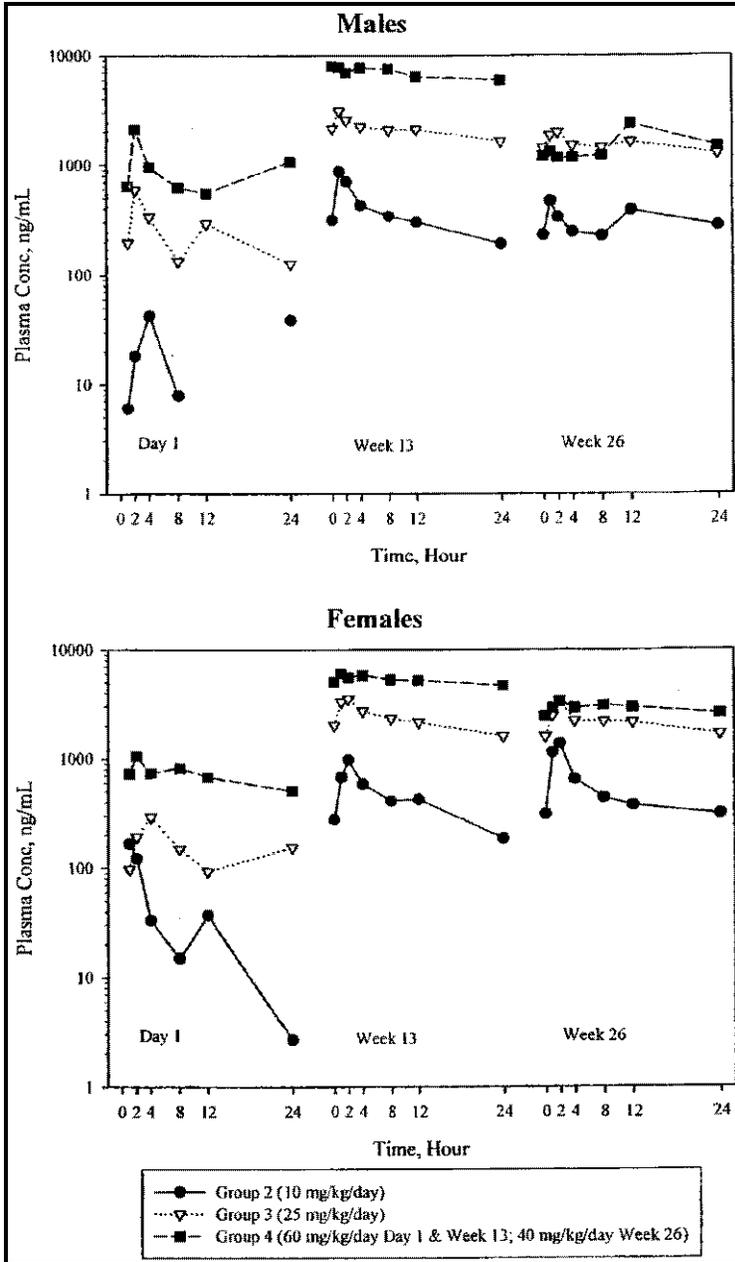
#### Female TK Parameters (Sponsor's Table)

Analyte	Parameter	Dose Group (mg/kg/day)								
		10 (Group 2)			25 (Group 3)			60 or 40 <sup>b</sup> (Group 4)		
		Day 1	Week 13	Week 26	Day 1	Week 13	Week 26	Day 1	Week 13	Week 26
C-1073	C <sub>max</sub> , ng/mL	190.9	1187.9	1398.6	396.9	3835.3	3771.0	1359.0	6417.4	3483.2
	T <sub>max</sub> <sup>a</sup> , h	1.0	2.0	2.0	24.0	2.0	2.0	5.0	2.5	1.5
	AUC(0-24), ng·h/mL	912.5	10195.4	11938.9	3638.5	54167.1	51114.8	16430.6	125596.8	69423.3
RU 42633	C <sub>max</sub> , ng/mL	100.3	450.6	576.0	232.5	1683.8	1546.7	679.8	3629.8	2179.5
	T <sub>max</sub> <sup>a</sup> , h	2.0	2.0	2.0	24.0	1.5	2.0	6.0	1.5	8.0
	AUC(0-24), ng·h/mL	551.6	5385.8	6099.1	2247.7	28724.7	27846.8	9287.4	77660.1	43790.7
RU 42698	C <sub>max</sub> , ng/mL	183.8	593.8	694.4	315.4	1538.8	1550.6	838.5	2718.0	1481.7
	T <sub>max</sub> <sup>a</sup> , h	2.0	4.0	2.0	24.0	4.0	10.0	10.0	4.0	10.0
	AUC(0-24), ng·h/mL	964.7	7932.2	9057.8	3211.3	28532.7	27516.6	11781.6	55473.0	31175.8
RU 42848	C <sub>max</sub> , ng/mL	55.2	154.1	194.6	111.7	683.2	749.3	249.1	1695.8	1096.3
	T <sub>max</sub> <sup>a</sup> , h	2.0	1.5	4.0	16.0	2.0	3.0	10.0	3.0	0.5
	AUC(0-24), ng·h/mL	376.1	2570.9	3272.8	1258.6	13727.2	14294.3	4285.7	36449.7	21232.6

<sup>a</sup> Expressed as median

<sup>b</sup> Dogs received 60 mg/kg/day for the first 16 weeks followed by 40 mg/kg/day thereafter due to toxicity

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**28-Day Toxicokinetic Study with C-1073 When Administered Once Daily by Oral Gavage to Cynomolgus Monkeys (T-006/2001-3623)**

5, 15, and 45 mg/kg (~0.01X, 0.05X, and 0.1X MRHD of 1200 mg/day; AUC basis)  
 Mortality, clinical signs, body weights, and TK data; study conducted primarily to assess the toxicokinetics of mifepristone.

Treatment-related emesis occurred during or immediately following dosing at ≥5 mg/kg.

Note: Although the high dose (45 mg/kg) did not produce frank toxicity, it was considered a MTD based upon a 1-month study where three of six monkeys administered 100 mg/kg were sacrificed moribund (vomiting, diarrhea, reduced appetite, and body weight loss) after

~2 weeks of dosing and a 6-month monkey study in which a dose of 45 mg/kg produced anti-progesterone and anti-glucocorticoid effects (Deraedt et al., 2011). Systemic exposure to mifepristone (907-1301 ng·h/mL) and its three major metabolites (RU42848 [6697-8349 ng·h/mL], RU42633 [2395-2438 ng·h/mL], and RU42698 [2019-2501 ng·h/mL]) at the high dose in this 1-month study (45 mg/kg) was only a fraction of that achieved in humans administered the MRHD of 1200 mg/day ( $\leq 0.3X$ ). Thus, the dog was selected as the nonrodent species for the chronic studies.

## 7 Genetic Toxicology

According to the approved label for Mifeprex<sup>®</sup> (mifepristone), a battery of genotoxicity studies conducted under NDA 20687 found no genotoxic potential for mifepristone: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pompe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice. To meet the requirements of ICH S2B (1997), the sponsor conducted two *in vitro* assays (Ames and chromosome aberration) to evaluate the genotoxicity of mifepristone. Mifepristone was not mutagenic or clastogenic in either assay.

### Bacterial Mutation Test

**Study No.:** T-009  
**Study Report Location:** Module 4; Volume 1.15  
**Conducting Laboratory and Location:** (b) (4)  
**Date of Study Initiation:** 25 August 2004  
**GLP Compliance:** Yes  
**QA Statement:** Yes  
**Drug, Lot #, and % Purity:** Mifepristone, lot 70295AA008, 99.4%

Mifepristone was tested using Salmonella and E.coli strains (with and without S9 mixture) up to a maximum concentration of 5000 µg/plate. The increase in revertant colony numbers were not 2 times greater than the concurrent negative controls with any bacterial strain in either the presence or absence of S9 mix. Under conditions of this assay, mifepristone was not mutagenic.

**Confirmatory Pre-Incubation Test in the Absence of S9 (Sponsor's Table)**

Strain	Conc. (µg/plate)	S9	Number of revertants					Plate observations *			Fold response †
			<i>x</i> <sub>1</sub>	<i>x</i> <sub>2</sub>	<i>x</i> <sub>3</sub>	mean	SD	<i>x</i> <sub>1</sub>	<i>x</i> <sub>2</sub>	<i>x</i> <sub>3</sub>	
TA1535	DMSO	0	15	30	13	<b>19</b>	9				1.0
	50	0	24	23	15	<b>21</b>	5				1.1
	158	0	15	22	8	<b>15</b>	7				0.8
	500	0	14	18	18	<b>17</b>	2	ppt	ppt	ppt	0.9
	1581	0	22	14	17	<b>18</b>	4	ppt	ppt	ppt	0.9
	5000	0	18	18	16	<b>17</b>	1	ppt	ppt	ppt	0.9
TA1537	DMSO	0	16	18	14	<b>16</b>	2				1.0
	15.8	0	8	13	9	<b>10</b>	3				0.6
	50	0	11	18	15	<b>15</b>	4				0.9
	158	0	13	11	11	<b>12</b>	1				0.7
	500	0	11	11	11	<b>11</b>	0	ppt	ppt	ppt	0.7
	1581	0	17	16	7	<b>13</b>	6	ppt	ppt	ppt	0.8
	5000	0	10	9	7	<b>9</b>	2	ppt	ppt	ppt	0.5 T
TA98	DMSO	0	25	25	28	<b>26</b>	2				1.0
	15.8	0	25	32	29	<b>29</b>	4				1.1
	50	0	23	39	21	<b>28</b>	10				1.1
	158	0	32	24	29	<b>28</b>	4				1.1
	500	0	22	23	33	<b>26</b>	6	ppt	ppt	ppt	1.0
	1581	0	15	21	23	<b>20</b>	4	ppt	ppt	ppt	0.8
	5000	0	11	13	13	<b>12</b>	1	ppt	ppt	ppt	0.5 T
TA100	DMSO	0	110	136	121	<b>122</b>	13				1.0
	15.8	0	107	102	118	<b>109</b>	8				0.9
	50	0	124	123	106	<b>118</b>	10				1.0
	158	0	111	142	115	<b>123</b>	17				1.0
	500	0	123	109	117	<b>116</b>	7	ppt	ppt	ppt	1.0
	1581	0	97	106	121	<b>108</b>	12	ppt	ppt	ppt	0.9
	5000	0	105	84	114	<b>101</b>	15	ppt	ppt	ppt	0.8
WP2 <i>uvrA</i>	DMSO	0	37	32	28	<b>32</b>	5				1.0
	50	0	23	22	24	<b>23</b>	1				0.7
	158	0	29	37	36	<b>34</b>	4				1.1
	500	0	31	33	34	<b>33</b>	2	ppt	ppt	ppt	1.0
	1581	0	28	21	22	<b>24</b>	4	ppt	ppt	ppt	0.7
	5000	0	30	33	21	<b>28</b>	6	ppt	ppt	ppt	0.9

\* Comments on the plate or background lawn if applicable: contamination (C), incomplete lawn (IL), no lawn (NL), not required (NR), poor lawn (PL), precipitate (ppt)

† Fold response in mean revertants compared to concurrent vehicle control

SD Sample standard deviation

T Toxic as indicated by low revertant colony counts (Fold response < 0.6), or incomplete/no background lawn (no meaningful count results for plates with IL or NL)

**Confirmatory Pre-Incubation Test in the Presence of S9 (Sponsor's Table)**

Strain	Conc. ( $\mu\text{g}/\text{plate}$ )	S9	Number of revertants					Plate observations *			Fold response †
			$x_1$	$x_2$	$x_3$	mean	SD	$x_1$	$x_2$	$x_3$	
TA1535	DMSO	+	20	22	20	21	1				1.0
	50	+	24	21	16	20	4				1.0
	158	+	10	18	17	15	4				0.7
	500	+	25	31	20	25	6				1.2
	1581	+	31	24	28	28	4				1.3
	5000	+	20	14	26	20	6	ppt	ppt	ppt	1.0
TA1537	DMSO	+	9	25	21	18	8				1.0
	50	+	15	14	18	16	2				0.9
	158	+	16	11	20	16	5				0.9
	500	+	6	13	10	10	4				0.5 A
	1581	+	21	22	10	18	7				1.0
	5000	+	9	11	16	12	4	ppt	ppt	ppt	0.7
TA98	DMSO	+	41	36	47	41	6				1.0
	50	+	38	36	34	36	2				0.9
	158	+	53	55	49	52	3				1.3
	500	+	36	43	41	40	4				1.0
	1581	+	40	39	41	40	1				1.0
	5000	+	41	36	29	35	6	ppt	ppt	ppt	0.9
TA100	DMSO	+	160	124	118	134	23				1.0
	50	+	126	161	136	141	18				1.1
	158	+	129	134	161	141	17				1.1
	500	+	137	103	128	123	18				0.9
	1581	+	141	147	115	134	17				1.0
	5000	+	103	115	144	121	21	ppt	ppt	ppt	0.9
WP2 <i>uvrA</i>	DMSO	+	41	25	25	30	9				1.0
	50	+	36	41	29	35	6				1.2
	158	+	41	24	40	35	10				1.2
	500	+	20	32	37	30	9				1.0
	1581	+	41	25	51	39	13				1.3
	5000	+	28	39	30	32	6	ppt	ppt	ppt	1.1

\* Comments on the plate or background lawn if applicable: contamination (C), incomplete lawn (IL), no lawn (NL), not required (NR), poor lawn (PL), precipitate (ppt)

† Fold response in mean revertants compared to concurrent vehicle control

SD Sample standard deviation

A Apparent decrease in colony count considered to be due to normal variation rather than indicative of toxicity; not outside historical range

**Chromosome Aberration Test**

**Study No.:** C-1073  
**Study Report Location:** Module 4; Volume 1.15  
**Conducting Laboratory and Location:** (b) (4)  
**Date of Study Initiation:** 25 August 2004  
**GLP Compliance:** Yes  
**QA Statement:** Yes  
**Drug, Lot #, and % Purity:** Mifepristone, lot 70295AA008, 99.4%

Primary cultures of human peripheral lymphocytes stimulated with phytohaemagglutinin from healthy, non-smoking male donors were exposed to mifepristone for either 4 hours (with and without S9) or 21 hours (without S9). The concentrations of mifepristone examined ranged from from 16-128  $\mu\text{g}/\text{mL}$  for the 4 hour treatment and 4-32  $\mu\text{g}/\text{mL}$  for the 21 hour treatment. For each treatment regime, the highest dose level of mifepristone selected for detailed analysis was that which produced at least a 50% decrease in the RMI (mitotic

index relative to the concurrent vehicle control). In addition, the highest dose levels were insoluble in the culture media Cyclophosphamide (with S9) and mitomycin C (without S9) were the positive controls. Mifepristone did not show any significant increases in chromosomal aberrations under any condition. Additionally, mifepristone did not cause any substantial increases in the incidence of chromatid or chromosome gaps, or polyploidy. The positive controls significantly increased chromosomal aberration confirming the sensitivity of the test system and the effectiveness of the S9 mix.

**Chromosomal Aberration Test using HPBL Cells (Sponsor's Table)**

Treatment	Conc. (µg/mL)	MI	RMI (%)	No. cells examined	% Aberrant	No. of aberrations					Incidental observations		
						b	e	B	E	other	g	G	P
<i>4 hours treatment in the absence of S9 (0S9)</i>													
DMSO	-	10.5	100	200	0.0	0	0	0	0	0	1	0	0
C-1073	16.0	7.4	70	200	0.5	1	0	0	0	0	4	0	0
	32.0	6.3	60	200	0.5	1	0	0	0	0	3	0	0
	64.0 ppt	5.7	54	200	0.5	1	0	0	0	0	1	1	0
	128 ppt	1.0	10	200	0.0	0	0	0	0	0	0	0	0
Mitomycin C	0.21 ‡	6.0	57	200	17.5**	20	12	8	0	0	11	2	0
<i>4 hours treatment in the presence of S9 (+S9)</i>													
DMSO	-	7.4	100	200	0.5	1	0	0	0	0	3	0	0
C-1073	32.0	6.6	89	200	0.5	1	0	0	0	0	3	1	0
	64.0 ppt	6.7	92	200	1.5	3	0	0	0	0	0	0	0
	128 ppt	2.6	36	200	0.0	0	0	0	0	0	0	0	0
Cyclophosphamide	12.0	3.1	42	200	29.5**	82	7	16	0	1	31	2	0
<i>21 hours treatment in the absence of S9 (0S9)</i>													
DMSO	-	7.5	100	200	1.0	2	0	0	0	0	1	0	0
C-1073	4.00	4.4	59	200	1.0	1	0	4	0	0	0	0	0
	8.00	5.0	66	200	0.0	0	0	0	0	0	1	0	0
	16.0	4.6	61	200	0.5	1	0	0	0	0	0	0	0
	32.0	0.8	11	200	0.0	0	0	0	0	0	0	0	0
Mitomycin C	0.10	5.7	76	200	18.0**	28	7	5	0	0	13	0	0

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- MI, RMI Mitotic Index, Relative Mitotic Index (vehicle = 100%)
- b, e, g Chromatid break, exchange, gap
- B, E, G Chromosome break, exchange, gap
- other Includes pulverized chromosomes and cells with > 8 aberrations
- P Polyploidy and endoreduplication
- † g, G and P are excluded from the calculation of % aberrant cells
- ‡ Concentration of Mitomycin C varies slightly from the concentrations of Mitomycin C listed in the protocol due to technical considerations at the time of the test
- ppt Precipitate visible in the culture medium

Results of statistical analysis using one-tailed Fisher's exact test

- \* p ≤ 0.01 (significant)
- \*\* p ≤ 0.001 (highly significant)
- otherwise p > 0.01 (not significant)

**8 Carcinogenicity**

The carcinogenic potential of mifepristone and its three metabolites were evaluated in 2-year studies in the mouse and rat.

**A 2-Year Oral Gavage Carcinogenicity Study of C-1073 in the Albino Rat (T-022)**

Study No.: T-022  
Study Report Location: Module 4; Volumes 27-42  
Conducting Laboratory and Location:  (b) (4)  
Date of Study Initiation: 22 April 2004  
GLP Compliance: Yes  
QA Statement: Yes  
Drug and Lot # (% Purity): Mifepristone, lots 70295AJ008 (100%), 70295AA011 (100.4%), and 70295AA012, (100.3%)  
CAC Concurrence: Yes (Nov 2003)

**Key Study Findings**Neoplastic Findings

- Hepatocellular adenomas increased in females with statistical significance by trend analysis and pair-wise comparisons at 125 mg/kg (high dose).
- Follicular cell adenomas, carcinomas, and pooled adenomas/carcinomas also increased in females with statistical significance by trend and pair-wise comparisons at 125 mg/kg.
- Mammary gland pooled adenoma/adenocarcinomas increased in females with statistical significance by trend and pair-wise comparisons at the mid dose (25 mg/kg) when the high dose is omitted from the trend analysis. Also marked dose-related decrease in fibroadenoma in all female dose groups (compared to controls).
- Historical control data were not submitted.

Non-Neoplastic Findings

- There was a treatment-related increase in retinal atrophy/degeneration at 125 mg/kg. Mechanism not established.
- Dose-related increases in follicular cell hypertrophy and follicular cell hyperplasia of the thyroid occurred at  $\geq 25$  mg/kg in males and females.
- Dose-related increases in the incidence and severity of hepatocellular hypertrophy occurred at all dose levels in males and females. Single cell necrosis, multinucleated hepatocytes, basophilic cell foci, and increased pigmentation also occurred in females. The severity and incidence of the liver findings generally correlates with the presence of tumors.
- Atrophy in the epididymis, prostate, and seminal vesicles as well as oligospermia in males at  $\geq 25$  mg/kg and uterine atrophy in females at  $\geq 5$  mg/kg are attributed to the pharmacodynamic activity of the drug.
- Adrenal cortical hypertrophy and increased adrenal weight in males and females at  $\geq 25$  mg/kg are also attributable to the pharmacodynamic activity of the drug.
- A dose-related increase in the incidence and severity of pulmonary histiocytosis occurred at  $\geq 25$  mg/kg.

### Maximum Clinical Exposure

1200 mg/day; 121 µg·h/mL (parent and 3 metabolites). The highest dose tested in this study achieved mean exposures near clinical exposure (0.6-1X MRHD).

### **Adequacy of Carcinogenicity Study**

The dose levels of 5, 25, and 125 mg/kg were based on the recommendation of the ECAC in November 2003; this study is considered acceptable. The high dose was recommended based on MTD in a 13-week dose ranging study (10-15% reduced BW gain). Though not discussed in the ECAC minutes, the sponsor employed identical dual vehicle controls in this study.

Highest exposure achieved in rats is approximately equal to therapeutic exposure in human subjects. As with mice, testing of higher doses was limited by toxicity in the rats, so further increases in exposure were not feasible. Liver and thyroid tumors were detected in rats which provide a tumor signal within the limited exposure range tested; however, the propensity for induction of tumors in other organs at exposures exceeding the clinical dose is not known. The usefulness of this study is thus limited by the low exposure achievable in rats.

### **Evaluation of Tumor Findings**

There was a significant increase in follicular cell adenomas and carcinomas of the thyroid and hepatocellular adenomas of the liver in the high dose females. The severity and incidence of several non-neoplastic findings in the liver (e.g., single cell necrosis, multinucleated hepatocytes, and basophilic cell foci) generally correlated with the presence of liver tumors. Hyperplasia (thyroid only) and hypertrophy were also noted in the liver and thyroid, mainly in the mid and high dose groups. Exposure in females was approximately twice that in males, which might explain the presence of tumors in the former. These findings occur in rats at exposures equal to and below exposure in human subjects.

Given that mifepristone tested negative in the standard genotoxicity battery, a non-genotoxic mechanism is likely responsible for the tumor development. The sponsor attributes the hepatocellular and follicular cell tumors to the rat-specific chronic induction of enzyme activity in the liver and a subsequent increase in thyroid hormone metabolism resulting in hyperplasia and eventually neoplasia (Wu and Farrelly, 2006). The rat rapidly metabolizes thyroxine due to a lack of thyroid hormone-binding globulin, which serves as a reserve in humans. This then causes a persistent elevation of TSH and subsequent hyperfunctioning/growth of the thyroid.

The sponsor did not conduct any mechanistic studies to assess thyroid function/activity or hepatic enzyme activity. Evidence in the published literature indicates that mifepristone causes CYP3A induction (Trubetskoy et al., 2005; Cui et al., 2005). However, the TK data show an increase in plasma drug levels in females over time in the 2-year bioassay, not a decrease as cited by the sponsor. Moreover, elevations in serum TSH and transient decreases in T4 (2-3 months) occurred in patients with meningioma treated with mifepristone (200 mg/day) for 20-40 months (Heikinheimo et al., 1997). Cases of hypothyroidism (↑ TSH and ↓ T4) also occurred in Cushing's patients in the clinical studies conducted in support of NDA 202107 (9 patients in Study 400; 5 patients in Study 415). Thus, it is not clear to what extent the neoplastic findings might be related to liver enzyme induction. The relevance to humans cannot be excluded.

Collectively, the mammary data are difficult to interpret given the marked decrease in fibroadenomas in all dose groups ( $\geq 5$  mg/kg) and the increase in adenomas/adenocarcinomas up to the mid dose (25 mg/kg). It is possible that a decrease in body weight at the high dose (15-17%) decreased the incidence of adenomas and pooled adenomas/adenocarcinomas at this dose. However, the pharmacological activity of the drug (i.e., anti-progesterone), decrease in fibroadenomas, and high background incidence of adenomas/adenocarcinomas make it difficult to conclude that mifepristone causes mammary adenomas/adenocarcinomas. In the 13-week rat study, there was duct and/or alveoli ectasia in mammary glands at all doses ( $\geq 25$  mg/kg;  $< 1X$  MRHD), but there were no other mammary findings in this study or the other pivotal subchronic or chronic studies in mice, rats or dogs.

<b>Methods</b>	
Doses:	0, 0, 5, 25, and 125 mg/kg/day
Frequency of Dosing:	Once daily
Dose Volume:	mL/kg
Route of Administration:	Oral (gavage)
Formulation/Vehicle:	0.2% Tween 80 and 0.25% Carboxymethylcellulose
Basis of Dose Selection:	MTD based upon decreased body weight/body weight gain (13-week study)
Species/Strain:	Rat/ Sprague Dawley (CrI:CD®(SD) IGS BR) (b) (4)
Number/Sex/Group:	Main: 60 TK: 12
Age:	6 weeks
Animal Housing:	Housed individually in stainless steel wire mesh-bottomed cages. The position of the cage racks was rotated within the animal room on a monthly basis.
Paradigm for Dietary Restriction:	Offered ~4-5 pellets/day of certified commercial laboratory diet (calorie restricted)
Dual Control Employed:	Two vehicle control groups
Interim Sacrifice:	None
Deviation from Study Protocol:	None

## Observations and Results

### Mortality

*Twice daily. Survival function for the dosing period estimated for each group using the Kaplan-Meier product-limit method applied on daily intervals.*

At the end of the treatment period, there was an increase in the preterminal mortality of males dosed at 125 mg/kg compared to controls. The sponsor identified significance of a positive dose-related trend in mortality rate for males ( $p=0.0154$ ; Peto's two-sided test). An independent FDA analysis identified a general decrease in the survival of males over dose, with the high dose group having the highest overall mortality compared to combined controls ( $p=0.002$ ).

Interestingly, females dosed at 125 mg/kg had the highest survival. The sponsor identified strong significance of a negative dose-related trend in mortality rate (p=0.0016) with a trend for increasing survival over increasing dose.

At least 26 animals in all dose groups survived to scheduled sacrifice.

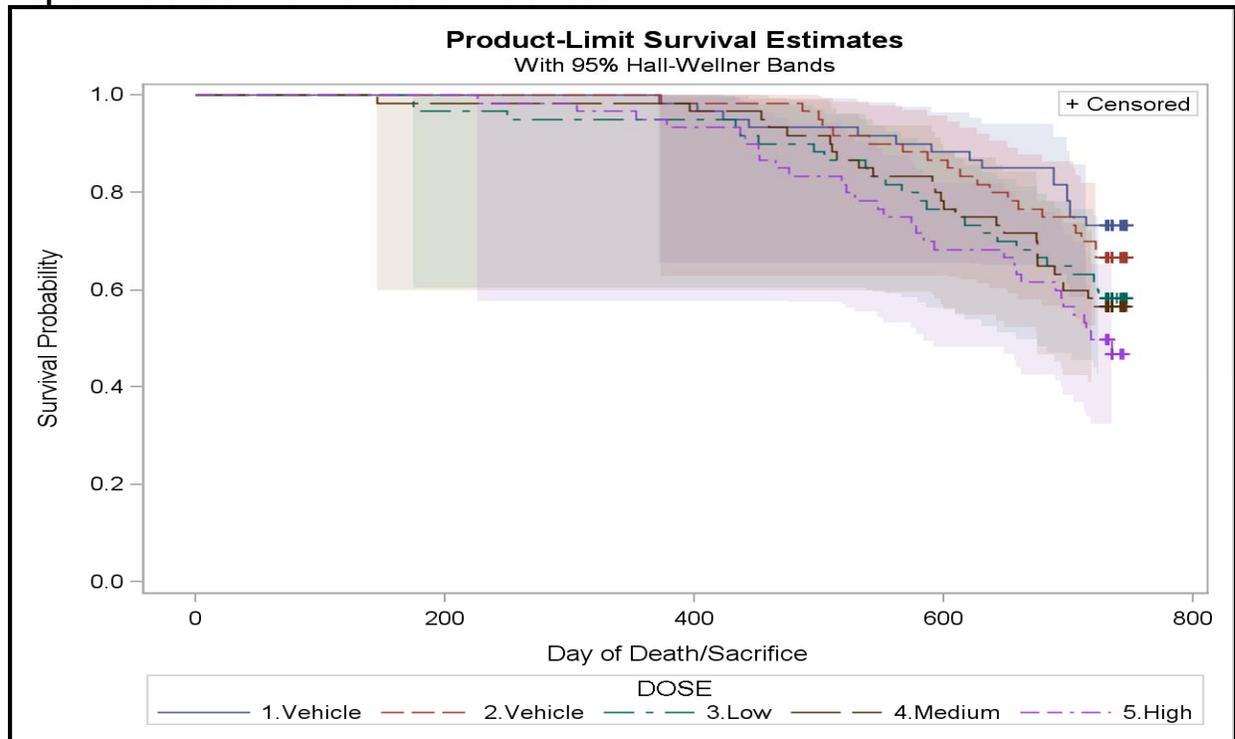
Although the most probable cause of death was determined for the majority of the preterminal decedents, there were no neoplastic or non-neoplastic causes attributable to treatment. In males and females, the most common cause of death was pituitary adenomas/carcinomas.

**Mortality and Survival (Sponsor's Table)**

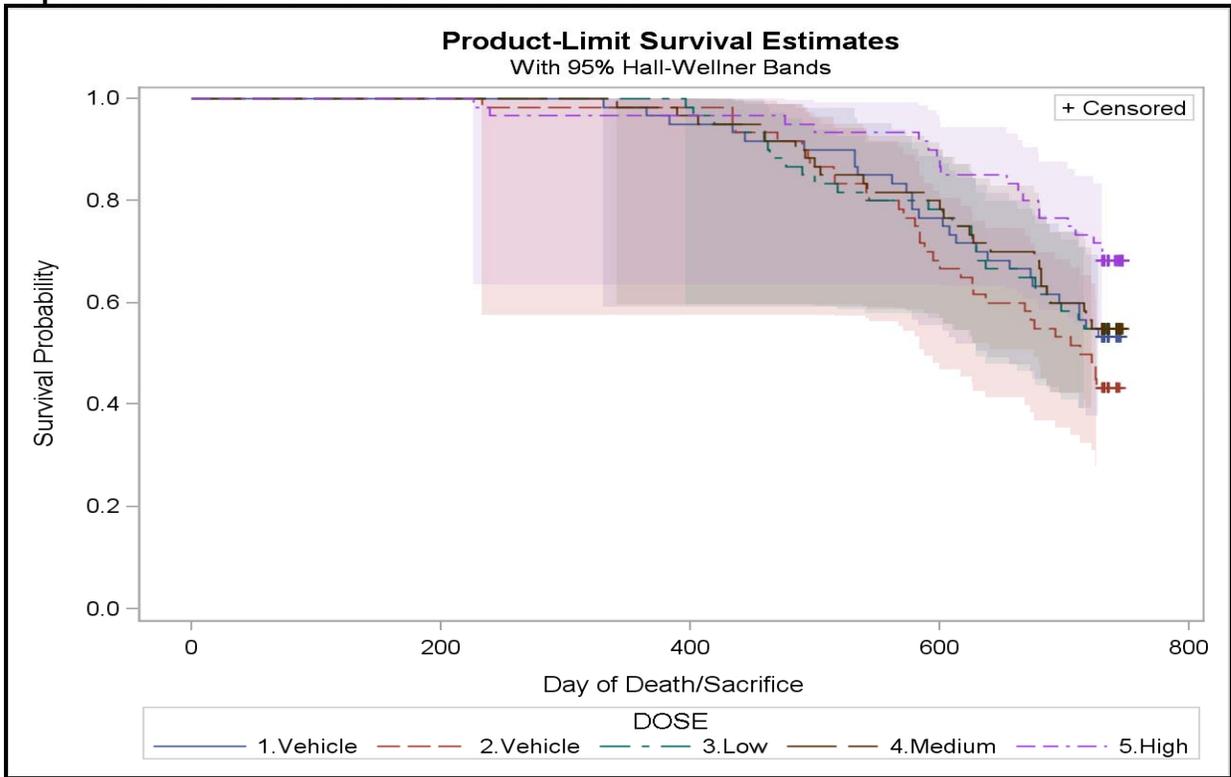
Group Number Identification	Male		Female	
	Mortality	Survival	Mortality	Survival
1/ Vehicle Control	16/60	73%	28/60	53%
2/ Vehicle Control	20/60	67%	34/60	43%
3/ C-1073	25/60	58%	27/60	55%
4/ C-1073	26/60	57%	27/60	55%
5/ C-1073	31/60	48%	19/60	68%

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**Kaplan-Meier Survival Curves for Male Rats**



**Kaplan-Meier Survival Curves for Female Rats**



**Major Factors Contributory to the Death/Preterminal Euthanasia (Weeks 1-106) (Sponsor's Table)**

Sex	Male					Female				
	0	0	5	25	125	0	0	5	25	125
Dose (mg/kg/day)	0	0	5	25	125	0	0	5	25	125
Number of animals examined	16	20	25	26	31	28	34	27	27	19
<i>Neoplastic Cause of Death</i>										
Pituitary adenoma/carcinoma	7	11	9	17	15	22	30	25	24	14
Hemolymphoreticular tumors	1	0	2	0	3	0	0	0	1	1
Mammary gland tumors	0	1	1	1	0	3	2	1	0	0
Subcutaneous Mesenchymal Tumors	1	1	1	3	1	0	0	0	0	1
Central Nervous System Tumors	2	1	1	1	1	0	0	0	0	0
Other Neoplastic Causes	1	4	3	1	3	2	1	1	1	1
<i>Non-Neoplastic Cause of Death</i>										
Chronic Progressive Nephropathy	1	0	0	0	1	0	0	0	0	0
Urinary Tract Lesions	1	0	2	0	0	0	0	0	0	0
Other non-neoplastic causes	0	1	2	1	1	0	0	0	0	0
<i>Undetermined Cause of Death</i>										
Undetermined Cause of Death	2	0	3	1	5	1	1	0	1	0
<i>Accidental (gavage accident, fracture)</i>										
Accidental (gavage accident, fracture)	0	1	1	1	1	0	0	0	0	2

**Clinical Signs**

*Main study animals. Weekly. Check for salivation performed daily pre- and post-dosing on the high dose male animals. Examined for the presence of palpable masses from Week 26 onward.*

There was a treatment-related increase in salivation (prior to and/or following dosing) in animals dosed at 125 mg/kg.

Treatment-related vaginal dilatation was also noted in approximately 22% of the females dosed at 125 mg/kg, which is attributable to the pharmacodynamic effect of the drug.

There was no treatment-related effect on the incidence, onset, or distribution of clinically observed masses at any dose level.

**Incidence of Clinically Observed Masses (Sponsor's Table)**

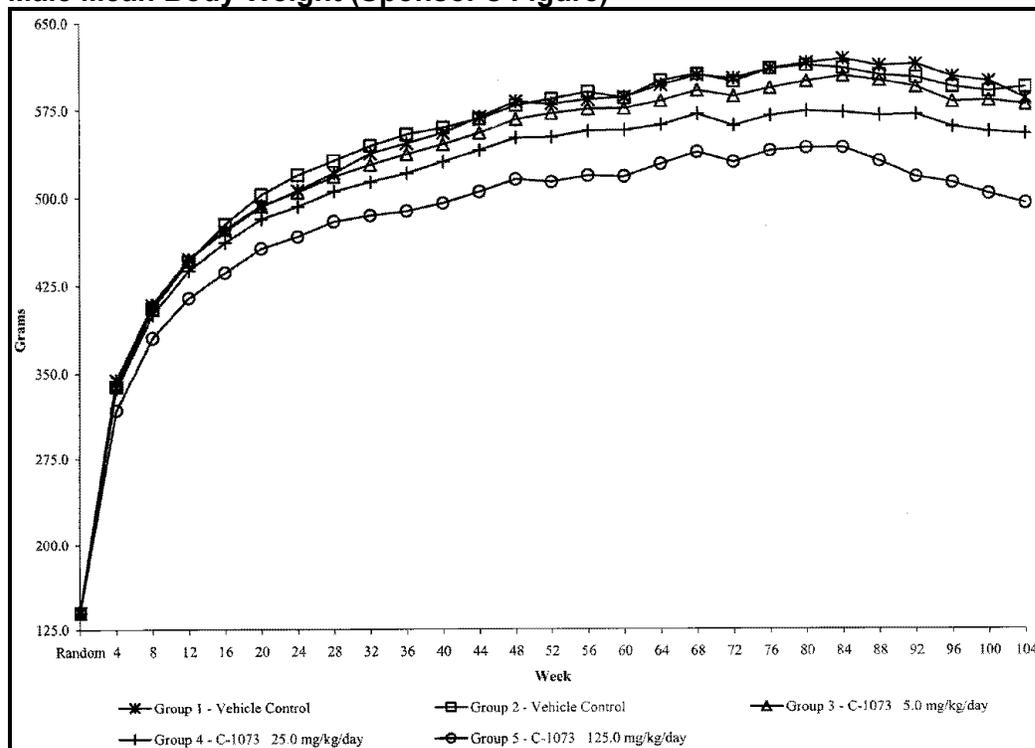
Group No. Identification	Dose Level (mg/kg/day)	Number of Animals with Masses			
		Males	%	Females	%
1/ Vehicle	0	11/60	18	35/60	58
2/ Vehicle	0	14/60	23	43/60	72
3/ C-1073	5.0	13/60	22	45/60	75
4/ C-1073	25.0	14/60	23	43/60	72
5/ C-1073	125.0	15/60	25	36/60	60

**Body Weights**

All animals. Pretest and weekly throughout treatment.

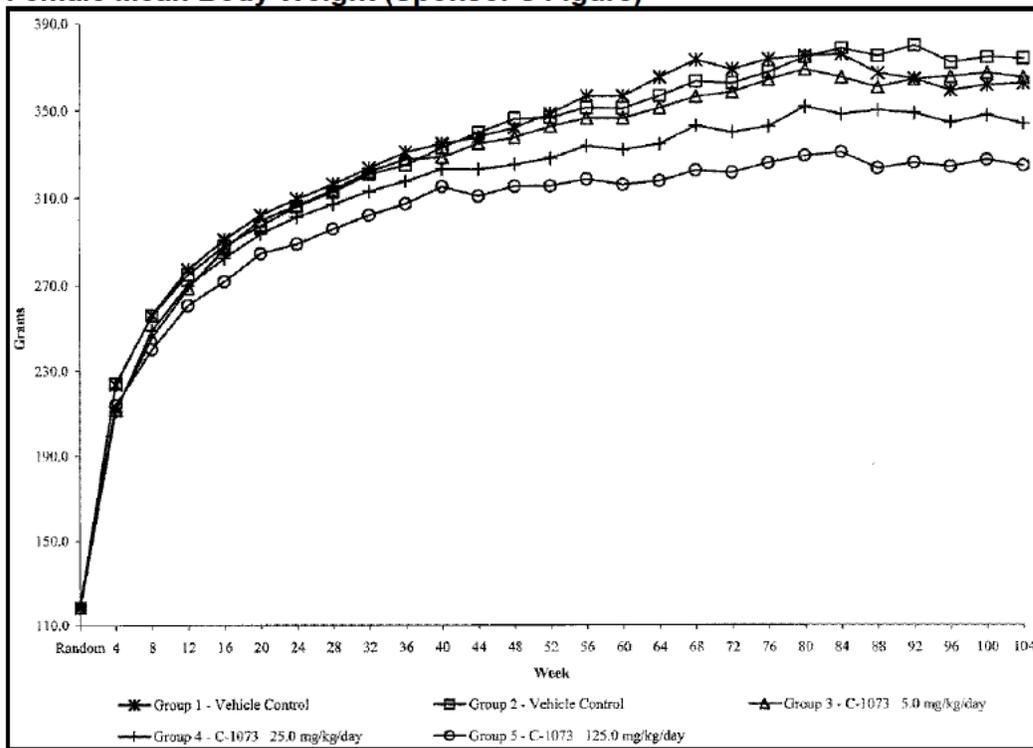
There was a dose-related decrease in body weight at all doses ( $\geq 5$  mg/kg) in males and females compared to controls, which did not correlate to a change in food consumption. Body weight was significantly ( $p < 0.05$ ) decreased (5-17%) in both males and females dosed at  $\geq 25$  mg/kg compared to controls. There was a statistically significant decrease in mean body weights in males dosed at 25 mg/kg from Week 4 onward and from Week 2 onward in males dosed at 125 mg/kg. Statistically significant reductions in body weight occurred in females dosed at  $\geq 25$  mg/kg from Week 1 onwards.

**Male Mean Body Weight (Sponsor's Figure)**



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**Female Mean Body Weight (Sponsor's Figure)**



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Body Weight						
Dose (mg/kg)	Males			Females		
	Pretest BW (g)	Wk 104 BW (g)	% Difference*	Pretest BW (g)	Wk 104 BW (g)	% Difference*
0	182.1	585.8	--	145.4	363	--
0	183	595.4	--	144.8	374.4	--
5	182.5	580.6	1-3%	145.9	365.6	1-2%
25	184.2	555.3	5-7%	144.4	344.6	5-8%
125	184.1	496	15-17%	144.2	324.2	11-13%

\* Percent difference from controls at Week 104

**Food Consumption**

Main study animals. Daily; recorded pellets remaining.

No treatment-related effects on food consumption.

**Ophthalmology**

All animals at pretest and all surviving main study animals prior to dosing, during Week 52, and Week 104. Funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations performed. Slides of fixed H&E-stained paraffin sections of the eyes for all main study animals that received a terminal ophthalmological examination were prepared and shipped to (b)(4), for a peer review of the histopathologic findings.

Slit lamp examinations yielded an increased incidence of diffuse retinal degeneration in females dosed at 125 mg/kg. Approximately 50% or more of the treated females with diffuse retinal degeneration had developed retinal degeneration by Week 52. In males dosed at 125 mg/kg at Week 104, there was a slightly increased incidence of cataracts, which was not statistically significant.

Slit Lamp Ophthalmologic Findings (n=60/group)										
Finding	Male (mg/kg)					Female (mg/kg)				
	0	0	5	25	125	0	0	5	25	125
Focal Chorioretinal Atrophy	2 (1)			2 (2)	1		2 (2)	1		2 (2)
Diffuse Retinal Degeneration		2			3 (1)	5 (2)	6 (1)	8 (4)	6 (4)	17 (8)

Shaded values indicate  $p < 0.01$  compared to control groups

( ) number of animals identified at Week 52

According to the sponsor, the affected animals were distributed in various rows of the racks, thus excluding disproportionate exposure of the high dose females to light as a causative factor for retinal degeneration. An unblinded peer review of the microscope slides of the globe and optic nerves of all the animals was conducted by ocular pathologists.

The microscopic examination revealed retinal atrophy in control males and particularly in control females, indicating that it is a background lesion. However, the incidence and severity of retinal atrophy increased in both males and females most clearly at the high dose. The retinal atrophy ranged from a decrease in photoreceptor cell bodies at the far periphery (minimal) to outer layer atrophy affecting a large part of the retina with retinal/choroidal vascular anastomosis (severe). The changes were not always symmetrical and were often segmental, but it is not possible to comment on the significance of this as the globes were not all sectioned in the same plane.

According to the ocular pathologists, the data indicate that the test article is affecting the "biologic systems that regulate the albino rodent-specific retinal atrophy phenomenon" given the treatment-related effect. FDA ophthalmology reviewers commented that it is difficult to tell if these nonclinical findings present additional clinical risk beyond that known when glucocorticoids are perturbed in human subjects.

Retinal Atrophy (n=60/group)										
	Male (mg/kg)					Female (mg/kg)				
	0	0	5	25	125	0	0	5	25	125
	60	60	59	60	60	60	60	60	60	60
Total Affected	1	7	10	15	27	30	35	31	33	44
Minimal	0	7	5	13	18	20	24	21	20	19
Moderate	1	0	3	1	6	6	10	5	9	11
Severe	0	0	2	1	3	4	1	9	4	14
Uninterruptable	3	2	4	6	12	6	8	1	5	7

### Hematology

All surviving main study animals at 12 and 18 months and at terminal necropsy. Red blood cell count and total and differential white blood cell counts.

At study termination, marked to severe increases in blood cell count (WBC), absolute neutrophils, absolute lymphocytes, and monocytes in females dosed at  $\geq 5$  mg/kg compared to controls. The increases were generally not dose-related but the levels increased with repeat dosing. Only lymphocytes showed a dose-related increase at study termination. Similar increases were not noted in the males.

### Female Hematology Parameters: Percent Difference from Controls (Sponsor's Table)

Parameters	Month 12			Month 18			Study Termination		
	Dose Level (mg/kg/day)			Dose Level (mg/kg/day)			Dose Level (mg/kg/day)		
	5	25	125	5	25	125	5	25	125
<b>WBC</b>									
Females	+35% <sup>b</sup>	+35%	+37%	+44%	+48%	+13%	+83%	+62%	+62%
	+14% <sup>c</sup>	+15%	+16%	+43%	+47%	+12%	+107%	+83%	+83%
<b>NEUT</b>									
Females	+58%	+62%	+54%	+75%	+87%	+18%	+144%	+94%	+76%
	+40%	+43%	+36%	+57%	+68%	+6%	+172%	+115%	+96%
<b>LYMPH</b>									
Females	+26%	+26%	+31%	+27%	+27%	+12%	+17%	+30%	+51%
	+7%	+7%	+11%	+35%	+35%	+19%	+31%	+46%	+69%
<b>MONO</b>									
Females	— <sup>a</sup>	—	+46%	—	—	—	+37%	+23%	+37%
			+8%				+105%	+83%	+105%

a Dash (—) indicates no compound-related difference from control values.

b The top value is compared to control Group 1.

c The bottom value is compared to control Group 2.

### Gross Pathology

All main study animals.

Macroscopic findings were noted in the adrenal gland (enlargement; 125 mg/kg), liver (enlargement/dark discoloration; 125 mg/kg), thyroid (enlargement; 125 mg/kg), lung (pale/raised area;  $\geq 25$  mg/kg), and male reproductive organs (small;  $\geq 25$  mg/kg). All the findings corresponded to microscopic findings discussed below.

**Macroscopic Findings (Sponsor's Table)**

Tissue/Finding Sex	Male					Female				
Dose (mg/kg/day)	0	0	5	25	125	0	0	5	25	125
Number of animals examined	60	60	60	60	60	60	60	60	60	60
<b>Adrenal</b>										
Enlargement	3	2	2	3	12	18	11	9	9	25
<b>Liver</b>										
Enlargement	2	2	4	3	13	1	1	0	2	2
Discoloration dark	1	0	0	0	3	0	1	1	1	30
<b>Thyroid</b>										
Enlargement/Mass	2	4	2	7	14	2	1	5	1	12
<b>Lung</b>										
Area raised/pale	10	8	6	19	36	7	6	14	23	44
<b>Epididymis</b>										
Small	2	3	4	7	15	NA	NA	NA	NA	NA
<b>Prostate</b>										
Small	2	3	1	5	21	NA	NA	NA	NA	NA
<b>Seminal Vesicle</b>										
Small	2	3	1	4	21	NA	NA	NA	NA	NA

NA = Not Applicable

**Histopathology**

*No peer review of neoplastic/non-neoplastic findings was conducted.*

**Neoplastic**

*All main study animals. All suspected tumors diagnosed, and the incidences of benign and malignant tumors of different cell types in the various treatment groups tabulated. The two control groups were pooled. Historical control data were not submitted.*

**Male Neoplasms (FDA Statistical Analysis)**

Organ/ Tumor	Incidence					Significance Levels				
	C1	C2	Low	Md	Hi	Trend	Hi vs C1+C2	Med vs C1+C2	Low vs C1+C2	
HEMOLYM. TISSUE										
# Evaluated	60	60	60	60	60					
Malignant lymphoma	0	0	0	1	2	.0265	.0914	.3137	.	
THYROID										
# Evaluated	60	60	60	60	60					
Adenoma/Carcinoma; Foll. cell	1	1	0	2	3	.0462	.1595	.3722	1	
Adenoma: follicular cell	1	0	0	1	3	.0213	.0809	.5304	1	

**Female Liver and Thyroid Neoplasms (FDA Statistical Analysis)**

Organ/ Tumor	Incidence					Significance Levels				
	C1	C2	Low	Md	Hi	Trend	Hi vs C1+C2	Med vs C1+C2	Low vs C1+C2	
LIVER										
# Evaluated	60	60	60	60	60					
Adenoma: hepatocellular	0	1	1	3	6	.0038	.0098	.1165	.5635	
THYROID										
# Evaluated	60	60	60	60	60					
Adenoma/Carcinoma; Foll. cell	0	1	3	1	11	<0.0001	.0001	.5698	.1122	
Adenoma: follicular cell	0	1	2	1	8	.0004	.0014	.5698	.2641	
Carcinoma: follicular cell	0	0	1	0	3	.0187	.0471	.	.3381	

**Female Mammary Neoplasms (FDA Statistical Analysis)**

	Incidence					Significance Levels				
	C1	C2	Low	Mid	High	C-H Trend	C-M Trend	H vs. C1+C2	M vs. C1+C2	L vs. C1+C2
<b>Tumor/Organ</b>										
<b>MAMMARY GLAND</b>										
<b># Evaluated</b>	59	60	59	59	60					
Adenocarcinoma	17	16	17	25	17	0.7056	0.0192	0.6618	0.0285	0.4354
Adenoma	9	12	23	24	16	0.5649	0.0057	0.1942	0.0022	0.0020
Adenoma/Adenocarcinoma	22	22	32	42	26	0.6871	<.0001	0.3527	<.0001	0.0140
Fibroadenoma	22	17	10	6	1	1	0.9989	1	0.9999	0.9938

Thyroid

In males and females, there was a statistically significant dose-response trend in follicular cell adenomas in the thyroid as identified by the sponsor (p=0.0142 [males]; p=0.0002 [female]) and an independent FDA statistical analysis (p=0.0213 [males]; p=0.0004 [female]). There was also a significant positive overall dose-response trend in follicular cell carcinomas and pooled adenomas/carcinomas in the thyroid of females (p<0.025).

However, only in females dosed at 125 mg/kg was there a statically significant increase in the incidence of follicular cell adenomas, follicular cell carcinomas, and pooled adenomas/carcinomas compared to the pooled controls (pair-wise comparison; p<0.05).

Liver

In females, in addition to a significant positive overall dose-response trend (p=0.0058 [sponsor]; p=0.0038 [FDA]), pair-wise comparison identified a statically significant increase in the incidence of hepatocellular adenomas in the high dose group (125 mg/kg) when compared to the pooled vehicle control groups in the sponsor's analysis (p=0.0130) and in the independent FDA statistical analysis (p=0.0098).

Mammary Glands

There was a marked dose-related decrease in the incidence of fibroadenomas in all female dose groups ( $\geq 5$  mg/kg), which is possibly a secondary effect of blocking the action of sex hormones. However, there was also an increased incidence of adenomas and pooled adenomas/adenocarcinomas of the mammary gland in the mid and low dose females compared to the pooled controls (p<0.01). When the high dose group was omitted from the trend analysis, there was a significant increase in the incidence of pooled adenomas/adenocarcinomas in females by trend (p<0.0001). It is possible that a decrease in body weight at the high dose (15-17%) decreased the incidence of adenomas and pooled adenomas/adenocarcinomas at this dose.

Hemolymphatic Tissue

Although there was a dose-response trend in males for hemolymphoreticular tissue malignant lymphomas (p=0.0247 [sponsor]; p=0.0265 [FDA]), the incidence in each treated group was not statistically greater than the pooled controls (pair-wise analysis).

*Four of the five animals with malignant lymphomas (lymphosarcomas) in the hemolymphoreticular tissue died prematurely; this was identified as the cause of death. Metastatic lymphomas were noted only in the high dose males with malignant lymphomas of the hemolymphoreticular tissue.*

## Non-Neoplastic

Microscopically, treatment-related non-neoplastic lesions were seen in adrenal gland, thyroid, liver, kidney, lung, epididymis, prostate, seminal vesicle, and uterus.

### Endocrine Organs: Thyroid and Adrenals

There was a dose-related increase in incidence and severity of follicular cell hypertrophy and follicular cell hyperplasia in males dosed at  $\geq 25$  mg/kg and females dosed at 125 mg/kg. The thyroid follicular cell hypertrophy/hyperplasia correlated with thyroid enlargement observed grossly. *In the 3-month rat study, an increase in thyroid weight was noted in females dosed at 125 mg/kg.*

In the adrenal glands, a dose-related increase in incidence and severity of cortical hypertrophy was observed in males and females dosed at  $\geq 25$  mg/kg. This change occurred in the zona fascicularis and reticularis and was likely attributable to an increase in ACTH (not measured). At 125 mg/kg, there was also a corresponding increase in the incidence of adrenal enlargement.

### **Endocrine Organ Microscopic Changes (Sponsor's Table)**

Tissue/Finding	Sex	Male					Female					
		0		5	25	125	0		5	25	125	
<b>Thyroid</b>	Number examined	60	60	60	60	60	60	60	60	60	60	
	Hypertrophy: follicular cell											
	Total Number affected	0	2	1	10	30	0	0	2	3	40	
	Minimal	—	2	1	8	8	—	—	2	3	9	
	Slight	—	—	—	2	22	—	—	—	—	31	
	Hyperplasia: follicular cell											
	Total Number affected	2	3	2	8	8	0	0	0	1	11	
	Minimal	1	—	—	1	1	—	—	—	—	2	
	Slight	—	1	1	4	5	—	—	—	1	6	
	Moderate	1	1	1	2	2	—	—	—	—	1	
	Marked	—	1	—	1	—	—	—	—	—	2	
<b>Adrenal</b>	Number examined	60	60	60	60	60	60	60	60	60	60	
	Hypertrophy: cortical											
	Total Number affected	1	4	4	9	18	0	1	1	14	20	
	Minimal	1	4	4	4	4	—	—	1	8	9	
	Slight	—	—	—	5	14	—	1	—	6	11	

### Liver

In males and females dosed at  $\geq 5$  mg/kg, there was an increase in the incidence and severity of hepatocellular hypertrophy, which mainly affected the centrilobular hepatocytes. As the severity increased, hepatocellular hypertrophy was also noted in the midzonal and periportal areas as well. The sponsor considered this to be an adaptive response reported with enzyme inducing agents, although enzyme induction was not assessed.

There was a dose-related increase (incidence and severity) in pigment deposition in males dosed at 125 mg/kg and females dosed at  $\geq 5$  mg/kg. The pigment, which was light brown to dark yellow in color, was mainly observed in portal and/or sinusoidal macrophages in control animals. In the drug-treated animals, pigment was observed in macrophages and the cytoplasm of hepatocytes. In animals dosed at 125 mg/kg, the increase in pigment correlated with the dark discoloration of the liver observed macroscopically. The sponsor did not attempt to characterize the pigment with different stains.

In females dosed at 125 mg/kg, single cell necrosis (minimal-moderate) was noted. Given that this change often affected scattered hepatocytes heavily loaded with pigment and occurred in animals with moderate to massive pigment deposits, the single cell necrosis maybe attributable to the pigment.

There was a dose-related increase in the incidence and severity of multinucleated hepatocytes in females dosed at  $\geq 5$  mg/kg. The multinucleated hepatocytes had an enlarged cytoplasm and contained multiple nuclei (more than two and up to twenty nuclei). There was also an increase in incidence and multiplicity of spontaneous basophilic cell foci in females dosed at  $\geq 25$  mg/kg. Both of these findings may be related to the incidence of hepatocellular adenomas in the high dose females.

### Liver Microscopic Changes (Sponsor's Table)

Tissue/Finding	Sex	Male					Female				
		0	0	5	25	125	0	0	5	25	125
<b>Liver</b>	Number examined	60	60	60	60	60	60	60	60	60	60
Hypertrophy: hepatocellular	Total Number affected	0	0	1	19	46	0	0	6	19	56
	Minimal	—	—	1	13	12	—	—	5	12	—
	Slight	—	—	—	5	21	—	—	1	7	4
	Moderate	—	—	—	1	13	—	—	—	—	18
	Marked	—	—	—	—	—	—	—	—	—	34
Deposits: pigment	Total Number affected	0	1	0	0	4	5	1	9	38	59
	Minimal	—	1	—	—	1	—	—	6	13	1
	Slight	—	—	—	—	3	4	—	2	17	8
	Moderate	—	—	—	—	—	1	1	1	8	28
	Marked	—	—	—	—	—	—	—	—	—	15
	Massive	—	—	—	—	—	—	—	—	—	7
Necrosis: single cell	Total Number affected	0	0	0	0	0	0	0	0	0	22
	Minimal	—	—	—	—	—	—	—	—	—	11
	Slight	—	—	—	—	—	—	—	—	—	10
	Moderate	—	—	—	—	—	—	—	—	—	1
Multinucleated hepatocytes	Total Number affected	0	0	0	0	0	0	1	5	15	49
	Minimal	—	—	—	—	—	—	1	4	8	6
	Slight	—	—	—	—	—	—	—	1	6	18
	Moderate	—	—	—	—	—	—	—	—	1	16
	Marked	—	—	—	—	—	—	—	—	—	9
Basophilic cell focus	Total Number affected	22	23	19	25	21	25	33	33	45	41
	Minimal	13	10	12	16	13	5	14	8	10	8
	Slight	5	7	6	6	5	10	13	13	17	20
	Moderate	2	5	1	3	2	6	5	9	9	10
	Marked	2	1	—	—	1	4	1	3	9	3
	Focal	8	10	10	12	12	9	11	9	3	8
	Multifocal	14	13	9	13	9	16	22	24	42	33

### Kidney

An increased incidence of pigment deposition in renal tubules was observed in females dosed at 125 mg/kg. *No information on the characteristics of the pigment was provided.*

**Kidney Microscopic Changes (Sponsor's Table)**

Tissue/Finding	Sex	Male					Female				
		0	0	5	25	125	0	0	5	25	125
Dose (mg/kg/day)		0	0	5	25	125	0	0	5	25	125
<b>Kidney</b>	Number examined	60	60	60	60	60	60	60	60	60	60
Deposits pigment: tubular											
	Total Number affected	0	0	0	2	2	3	1	9	5	17
	Minimal	—	—	—	2	—	2	1	3	4	8
	Slight	—	—	—	—	2	1	—	5	1	7
	Moderate	—	—	—	—	—	—	—	1	—	2

**Lung**

A dose-related increase in the incidence and severity of pulmonary histiocytosis was observed in males and females dosed at  $\geq 25$  mg/kg. This finding was characterized by accumulation of foamy histiocytes in alveoli, frequently around bronchioles and uncommonly under the pleura. It was also sometimes associated with accumulation of alveolar eosinophilic material and correlated with pulmonary pale/raised area observed macroscopically.

**Lung Microscopic Changes (Sponsor's Table)**

Tissue/Finding	Sex	Male					Female				
		0	0	5	25	125	0	0	5	25	125
Dose (mg/kg/day)		0	0	5	25	125	0	0	5	25	125
<b>Lung</b>	Number examined	60	60	60	60	60	60	60	60	60	60
Histiocytosis											
	Total Number affected	13	16	12	27	42	20	12	22	34	49
	Minimal	9	13	8	21	19	15	11	17	18	16
	Slight	2	2	3	5	18	5	1	3	11	20
	Moderate	2	1	1	1	5	—	—	1	5	12
	Marked	—	—	—	—	—	—	—	1	—	1

**Reproductive Organs**

There was a dose-related increase in the incidence and severity of atrophy in the epididymis, prostate, and seminal vesicle of males dosed at  $\geq 25$  mg/kg. The atrophy was characterized by a general reduction in size and decreased luminal secretion in the prostate and seminal vesicle. There was a slight increase in the severity of oligospermia associated with epididymal size decrease in males dosed at  $\geq 25$  mg/kg. These changes in the epididymis, prostate and seminal vesicle are compatible with those associated with androgen levels reduction or receptor blockage.

**Male Reproductive Organ Microscopic Changes (Sponsor's Table)**

Tissue/Finding	Sex	Male				
		Dose (mg/kg/day)				
		0	0	5	25	125
<b>Epididymis</b>	Number examined	60	60	59	60	60
Atrophy	Total Number affected	5	11	6	14	30
	Minimal	2	4	—	3	7
	Slight	3	5	3	4	14
	Moderate	—	2	2	5	9
	Marked	—	—	1	2	—
<b>Prostate</b>	Number examined	60	60	60	60	60
Atrophy	Total Number affected	6	6	1	22	54
	Minimal	—	2	—	5	8
	Slight	4	1	—	15	28
	Moderate	1	3	—	2	18
	Marked	1	—	1	—	—
<b>Seminal Vesicle</b>	Number examined	60	60	60	60	60
Atrophy	Total Number affected	3	7	2	19	45
	Minimal	—	3	1	6	12
	Slight	2	3	—	12	23
	Moderate	1	1	1	1	10

In females dosed at  $\geq 5$  mg/kg, there was a dose-related increase in the incidence and severity of uterine atrophy (minimal-marked) compared to both vehicle control groups. Atrophy in vehicle control animals was characterized by a uniform decrease in uterine layers thickness (endometrium, myometrium and perimetrium) with the endometrial stroma containing dense collagenous fibers. However, uterine atrophy in the mifepristone-treated females was characterized by a reduction in the height of the endometrial stroma with a reduced amount of dense collagenous fibers.

**Female Reproductive Organ Microscopic Changes (Sponsor's Table)**

Tissue/Finding	Sex	Female				
		Dose (mg/kg/day)				
		0	0	5	25	125
<b>Uterus</b>	Number examined	59	60	60	60	60
Atrophy	Total Number affected	10	11	45	53	57
	Minimal	2	4	3	5	1
	Slight	6	5	12	18	20
	Moderate	2	2	19	21	24
	Marked	—	—	11	9	12

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**Toxicokinetics**

*Pre-dose and at 1, 2, 4, 6, 12, and 24 hours post-dose on Days 1 and end of Week 26.*

Mifepristone (C-1073) was metabolized into RU42633, RU42698, and RU42848. Metabolism was generally rapid with the detection of metabolite plasma concentrations within 1-2 hours of mifepristone administration, although peak plasma concentrations of RU42698 and RU42848 occurred 4-12 hours post-dose at the high dose. Exposure ( $C_{max}$  and  $AUC_{0-24}$ ) increased with dose for all four analytes. RU42848 systemic exposure was highest in both sexes across all dose groups.

Overall, exposures ( $AUC$  and  $C_{max}$ ) to mifepristone and its 3 metabolites were appreciably higher in female rats as compared to males following both single and multiple doses. With repeat dosing, exposure ( $AUC$  and  $C_{max}$ ) increased with repeated dosing in males dosed

at  $\leq 25$  mg/kg and females dosed at 5 mg/kg. However, changes in exposure of the four analytes following repeat dosing were variable at higher doses (125 mg/kg [males];  $\geq 25$  mg/kg [females]) likely due to the complex pharmacokinetics of mifepristone.

After 26 weeks of dosing, animals administered 5, 25, and 125 mg/kg mifepristone achieved exposures of  $\sim 0.02$ - $0.05X$ ,  $0.2$ - $0.3X$ , and  $0.6$ - $1X$  the MRHD of 1200 mg/day (AUC basis; parent and 3 metabolites), respectively.

#### TK Parameters of Male Rats (Sponsor's Table)

Analyte	Parameter	Dose Group (mg/kg/day)					
		5		25		125	
		Day 1	Week 26	Day 1	Week 26	Day 1	Week 26
C-1073	Cmax, ng/mL	30.6	69.6	374.0	497.4	1498.5	808.6
	Tmax, h	1.0	1.0	1.0	1.0	1.0	4.0
	AUC(0-24), ng-h/mL	68.0	163.5	1572.8	1677.6	12492.9	9310.4
RU 42633	Cmax, ng/mL	21.6	173.9	746.3	1282.4	2138.7	1117.2
	Tmax, h	1.0	1.0	1.0	1.0	2.0	4.0
	AUC(0-24), ng-h/mL	76.6	667.2	2383.9	4810.2	19266.6	14134.2
RU 42698	Cmax, ng/mL	17.8	77.0	405.1	978.3	1546.5	2404.7
	Tmax, h	4.0	1.0	1.0	1.0	4.0	4.0
	AUC(0-24), ng-h/mL	58.3	224.0	1345.8	3358.5	14653.0	18793.7
RU 42848	Cmax, ng/mL	122.8	325.7	868.0	1515.3	2426.6	1900.7
	Tmax, h	4.0	2.0	1.0	1.0	4.0	4.0
	AUC(0-24), ng-h/mL	343.5	1222.1	3448.5	8740.2	23188.0	33326.8

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#### TK Parameters of Female Rats (Sponsor's Table)

Analyte	Parameter	Dose Group (mg/kg/day)					
		5		25		125	
		Day 1	Week 26	Day 1	Week 26	Day 1	Week 26
C-1073	Cmax, ng/mL	289.1	368.7	1657.7	1323.1	3467.0	4425.0
	Tmax, h	1.0	1.0	1.0	1.0	1.0	1.0
	AUC(0-24), ng-h/mL	486.2	1086.1	7760.5	6365.1	21263.9	26334.9
RU 42633	Cmax, ng/mL	211.9	417.4	831.4	1034.2	1373.2	2966.0
	Tmax, h	1.0	1.0	2.0	1.0	1.0	1.0
	AUC(0-24), ng-h/mL	380.2	1594.6	4465.3	6873.8	13678.9	26534.5
RU 42698	Cmax, ng/mL	388.1	401.8	2335.7	1779.3	3921.4	4473.4
	Tmax, h	1.0	1.0	2.0	1.0	6.0	2.0
	AUC(0-24), ng-h/mL	718.3	1283.3	13498.4	11364.8	34884.6	45762.3
RU 42848	Cmax, ng/mL	291.5	401.0	654.7	891.0	1102.0	4271.4
	Tmax, h	1.0	1.0	2.0	4.0	12.0	4.0
	AUC(0-24), ng-h/mL	817.8	2272.9	5376.5	9315.5	16538.5	64214.7

#### Dosing Solution Analysis

All study samples analyzed were within the acceptance criteria of  $\pm 10\%$  of their nominal concentrations. The system suitability, linearity and accuracy evaluations for the dose formulation analysis were within the acceptance criteria of the analytical methods. Measured concentrations of mifepristone in the dose formulations deviated from nominal concentrations by a maximum of 5.1%.

**104-Week Oral Oncogenicity Study of C1073 in Mice (T-014/950-005)**

**Study Title:** 104-Week Oral Oncogenicity Study of C1073 in Mice  
**Study No.:** T-014/950-005  
**Study Report Location:** Module 4; Volumes 20-27  
**Conducting Laboratory and Location:** (b) (4)  
**Date of Study Initiation:** 31 August 2004  
**GLP Compliance:** Yes  
**QA Statement:** Yes  
**Drug, Lot #, and % Purity:** Mifepristone, lot 70295AR002, 98.6%  
**CAC Concurrence:** Yes; see below

**Key Study Findings**Neoplastic Findings

- No statistically significant tumors were found in males or females.

Non-Neoplastic Findings

- Survival was reduced for females dosed at 300 mg/kg and 200 mg/kg resulting in the reduction of the dose level to 125 mg/kg at Week 54.
- A dose-related decrease in uterine weights corresponded with uterine atrophy and a decrease in the incidence and severity of cystic endometrial hyperplasia in all mifepristone treatment groups.
- A decrease in ovary weight at  $\geq 100$  mg/kg, like the effects on the uterus, is attributable to the pharmacodynamic activity of the drug.

Maximum Clinical Exposure

1200 mg/day; 121  $\mu\text{g}\cdot\text{h}/\text{mL}$  (parent and 3 active metabolites). The high dose tested in males (125 mg/kg) and females (125 mg/kg) in this study only achieved exposures near clinical exposure ( $\sim 0.6\text{X}$  MRHD). Although the highest dose in females (300 mg/kg) at Week 26 achieved exposure of  $\sim 2\text{X}$  the MRHD, exposure at the final high dose of 125 mg/kg (Week 54 onward) is likely to approximate exposure at the mid dose (100 mg/kg;  $0.5\text{X}$  MRHD)

**Adequacy of Carcinogenicity Study**

The sponsor followed ECAC's recommended doses for male and female mice, and therefore this study is considered acceptable. The high dose of 125 mg/kg in male mice was based on reduced BW gain in a 13-week study, whereas the high dose of 300 mg/kg in female mice was based on deaths at 750 mg/kg in a 1-month study. Concurrence was communicated in 2004.

Exposures at the doses tested in mice are less than clinical exposure. While this study is considered acceptable, it is hard to argue that the study provides an 'adequate' assessment of carcinogenicity because of the (necessary) limitation of dosing in mice. Dosing of mifepristone in mice is limited by toxicology, so further increases in drug exposure are not feasible. The 'negative' tumor finding in mice is tempered by the limited

exposure achieved in the study, and therefore provides little assurance that mifepristone is devoid of tumorigenic potential.

### **Evaluation of Tumor Findings**

There were no tumor increases in any treatment group that were considered to be treatment-related or biologically significant. Given the excessive premature mortality at the high dose, the sponsor conducted a full histopathological assessment of the low and mid dose groups (male and female) including all premature decedents and mice sacrificed at termination as requested by the by the Division of Psychiatric Products in June 2009.

<b>Methods</b>	
Doses:	Males: 0, 12.5, 65, and 125 mg/kg/day Females: 0, 25, 100, and 300/200/125 mg/kg/day
Frequency of Dosing:	Once daily
Dose Volume:	10 mL/kg
Route of Administration:	Oral (gavage)
Formulation/Vehicle:	0.25% carboxymethylcellulose and 0.2% Tween 80 in sterile water for injection, USP
Basis of Dose Selection:	Males: decrease in body weight gain at 125 mg/kg (13-week study) Females: lack of dose-limiting toxicity at 500 mg/kg and deaths at $\geq 750$ mg/kg (1-month study)
Species/Strain:	Mouse/Crl:CD-1(ICR)BR [REDACTED] (b) (4)
Number/Sex/Group:	Main: 60 TK: 50
Age:	~8 weeks
Animal Housing:	Suspended, stainless steel, wire-mesh type cages in an environmentally controlled room; fluorescent lighting 12 hours/day
Paradigm for Dietary Restriction:	None
Dual Control Employed:	None
Interim Sacrifice:	None
Satellite Groups:	8/sex/group as possible replacement animals
Deviation from Study Protocol:	Due to the high incidence of mortality in the main study 300 mg/kg female group (main group), the dose level was decreased to 200 mg/kg beginning in Week 36, and the dose level was decreased again to 125 mg/kg beginning in Week 54; the 300 mg/kg dose in the female TK group was not decreased during the study. A full histopathological assessment of the low and mid dose groups (male and female) including all premature decedents and mice sacrificed at termination was conducted due to excessive premature death in the high dose groups; examination of the low/mid dose groups based on a request from DPP (June 2009).

## Observations and Results

### Mortality

*Twice daily. Third evening cageside observation added beginning in Week 53.*

Survival for males at all dose levels and females up to 100 mg/kg were comparable to controls during the first 18 months of study. Mortality in females dosed at 300 mg/kg was increased resulting in the reduction of the dose level to 200 mg/kg at Week 36. A

subsequent dose reduction to 125 mg/kg was required at Week 54 due to high mortality. At 125 mg/kg, female survival was comparable to control.

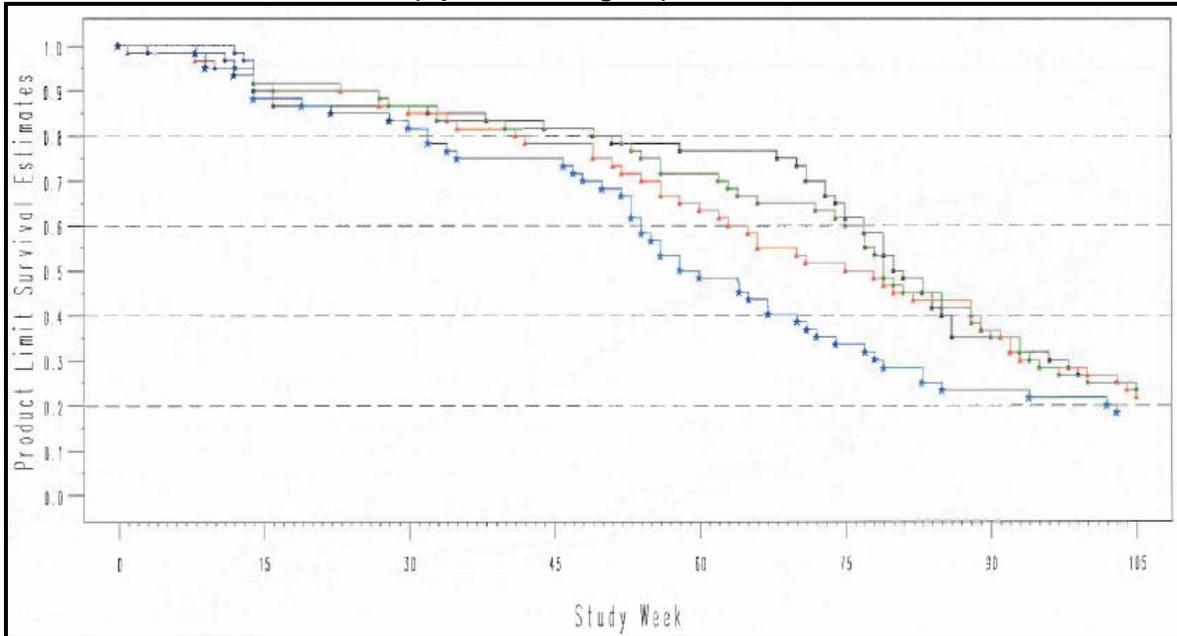
Survival of males at the terminal necropsy was 15, 13, 14, and 11 in the control and 12.5, 65, and 125 mg/kg groups, respectively. Survival of females at the terminal necropsy was 14, 20, 19, and 9 in the control and 25, 100, and 300/200/125 mg/kg groups, respectively.

Dose reductions in the females were done with concurrence by the ECAC. There was weak evidence in males and strong evidence in females of early death without tumors.

Causes of Mortality

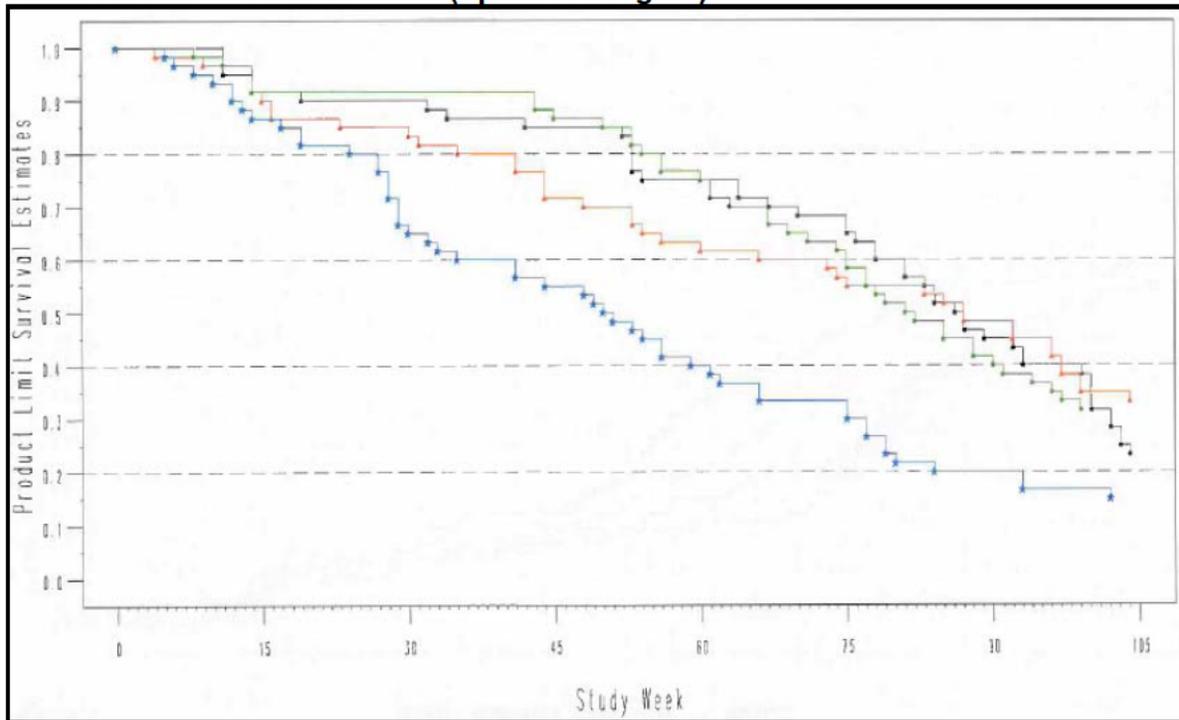
There was no obvious treatment-related cause of death. The most common cause of death was undetermined or amyloidosis. Uterus inflammation/necrosis was the cause of death of two females in the 300/200/125 mg/kg group; not identified in any other group.

**Male Mean Survival Estimate (Sponsor's Figure)**



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**Female Mean Survival Estimate (Sponsor's Figure)**



**Survival at Termination (Week 105; Study Initiated with 60/Group)**

Sex (Doses)	Vehicle	LD	MD	HD
Males (12.5, 65, 125 mg/kg)	15	13	14	11
Females (25, 100, 300/200/125mg/kg)	14	20	19	9

**Clinical Signs**

*Main study animals. Weekly.*

No treatment-related clinical signs. The occurrences of masses in males and females were either similar between control and treated animals for both genders or occurred in a minimal number of animals such that no apparent difference was evident.

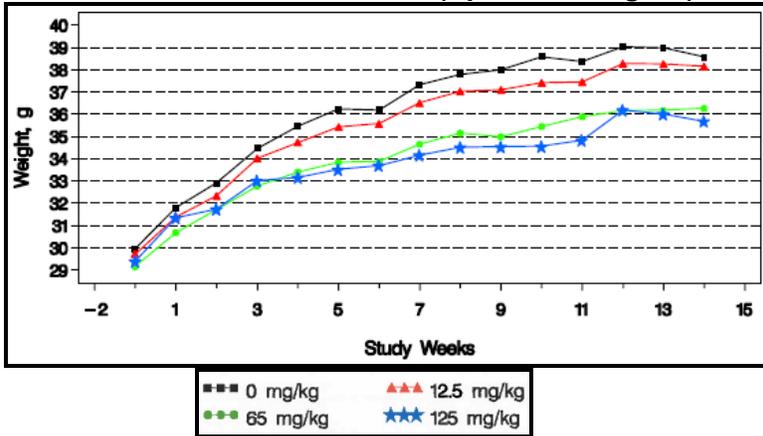
**Body Weights**

*All animals. Pretest, weekly for the first 14 weeks, every two weeks until Week 32, and every four weeks thereafter.*

Overall, drug-treated animals gained less weight than vehicle-treated animals. Final body weights were ~10% less than control and are not considered excessive.

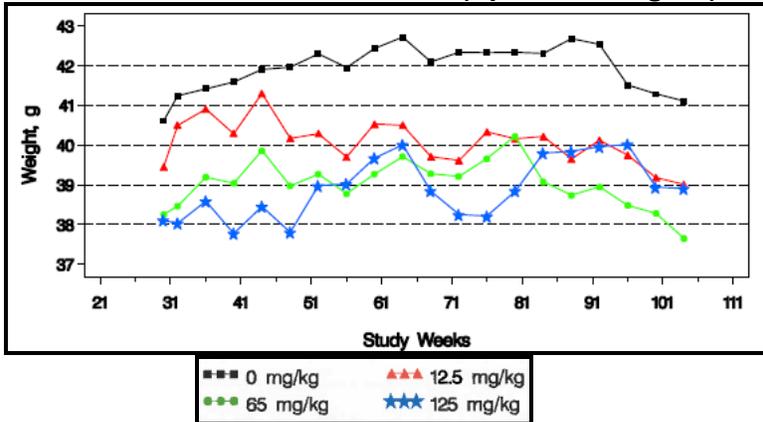
Male mice gained less body weight in a dose-related manner throughout the study; at termination, dosed groups weighed approximately 10% less than control, but without a clear dose dependence.

**Male Mean BW: Weeks -1 to 14 (Sponsor's Figure)**



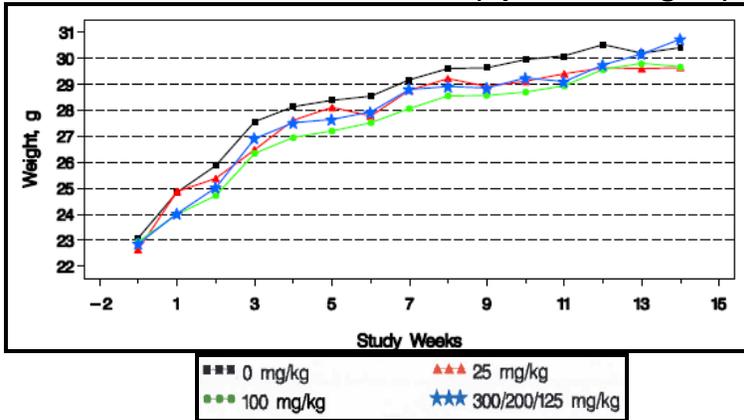
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**Male Mean BW: Weeks 31 to 105 (Sponsor's Figure)**



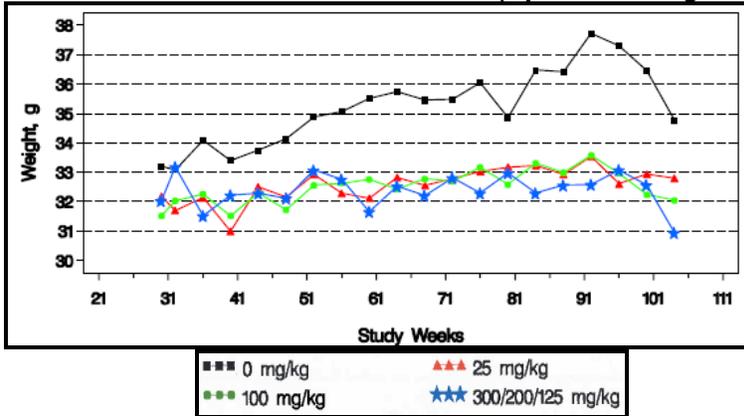
Female mice gained less weight after Week 15 of the study, with all dosed groups weighing approximately 10% less than controls by study termination at Week 105.

**Female Mean BW: Weeks -1 to 14 (Sponsor's Figure)**



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**Female Mean BW: Weeks 31 to 105 (Sponsor's Figure)**



**Food Consumption**

Main study animals. Weekly for the first 14 weeks, every two weeks until Week 32, and every four weeks thereafter.

No treatment-related effect on food consumption.

**Ophthalmology**

All animals at pretest and all surviving main study animals prior to the terminal necropsy. Slides of fixed H&E-stained paraffin sections of the eyes for all main study animals that received a terminal ophthalmological examination were prepared and shipped to (b) (4), for a peer review of the histopathologic findings.

Although there were an “excessively high number of abnormalities” noted by the ophthalmologist, none of the findings were considered to be treatment-related. Abnormal ophthalmoscopic observations at the terminal examination of each male group were 53%, 71%, 73%, and 82% in the control and 12.5, 65, and 125 mg/kg groups, respectively. Abnormal ophthalmoscopic observations at the terminal examination of each female group

were 80%, 76%, 89%, and 78% in females in the control and 25, 100, and 300/200/125 mg/kg groups, respectively. There were no treatment-related observations of retinal atrophy or degeneration in the ophthalmoscopic examinations.

Given the treatment-related increase in the incidence of diffuse retinal degeneration identified by ophthalmologic slit-lamp examination at Weeks 52 and 104 in female rats dosed at 125 mg/kg in the 2-year rat study, the microscope slides of the globe and optic nerves from all mice of the 2-year study were examined by ocular pathologists. This unblinded peer review identified a few cases of retinal atrophy ranging minimal to severe in mice that did not appear to be treatment-related. However, there was a high incidence of autolyzed retina in the unscheduled deaths made the findings difficult to interpret.

**Hematology**

*Fifteen main study animals/sex/group at pretest and during months 3, 6, 12, and 18, as well as all surviving main study animals prior to the terminal necropsy and any main study animals euthanized in extremis. Leukocytes, erythrocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, large unstained cells.*

In males dosed at ≥12.5 mg/kg, there was a dose-related increase in leukocytes (77-81% ↑), neutrophils (302-512% ↑), and monocytes (196-294% ↑) relative to pretest values. There were no notable treatment-related hematology changes in females.

**Male Hematology Parameters (Sponsor’s Table)**

Endpoint	Interval of Study	0 mg/kg			12.5 mg/kg			65 mg/kg			125 mg/kg		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Leukocytes 10 <sup>3</sup> /μL	Pretest	6.31	2.022	9	5.41	1.124	12	6.34	0.990	11	5.89	2.275	8
	3 Month	7.82	3.698	15	7.17	0.994	12	6.01	1.585	13	6.18	1.760	12
	6 Month	7.86	6.329	14	4.14	2.122	13	3.87	1.626	12	4.88	2.774	12
	12 Month	7.49	3.787	15	6.04	3.412	15	6.70	6.172	15	5.49	2.153	15
	18 Month	9.68	7.497	15	6.44	4.039	15	6.01	2.048	13	6.64	3.135	15
	Terminal	7.75	1.869	15	9.55	3.083	13	10.33	4.318	14	10.65	10.315	11
Neutrophils 10 <sup>3</sup> /μL	Pretest	0.817	0.2570	9	0.697	0.1837	12	0.847	0.2038	11	0.770	0.4194	8
	3 Month	1.746	2.0607	15	1.125	0.4022	12	1.022	0.4129	13	1.102	0.4554	12
	6 Month	3.659	5.0216	14	1.032 <sup>b</sup>	1.2220	13	0.999	0.9180	12	1.731	1.8041	12
	12 Month	3.091	2.2312	15	2.290	2.4294	15	2.533	3.6303	15	2.052	1.2928	15
	18 Month	3.869	4.2473	15	2.075	1.2319	15	2.032	1.5424	13	2.550	2.1479	15
	Terminal	2.639	1.0737	15	2.798	1.2875	13	4.147	2.9885	14	4.709	6.4230	11
Monocytes 10 <sup>3</sup> /μL	Pretest	0.143	0.0675	9	0.084	0.0759	12	0.145	0.0664	11	0.066	0.0682	8
	3 Month	0.206	0.1615	15	0.143	0.0538	12	0.134	0.0552	13	0.125	0.0688	12
	6 Month	0.196	0.1663	14	0.115	0.0609	13	0.100	0.0473	12	0.116	0.0838	12
	12 Month	0.165	0.1065	15	0.123	0.0509	15	0.118	0.0549	15	0.111	0.0975	15
	18 Month	0.185	0.1541	15	0.097	0.1137	15	0.117	0.1052	13	0.129	0.1421	15
	Terminal	0.241	0.0861	15	0.249	0.0877	13	0.335	0.2022	14	0.260	0.1348	11

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**Organ Weights**

*All surviving main study animals at necropsy; organs will not be weighed for animals dying spontaneously or euthanized in extremis. Absolute weight, weight as a percent of body weight, and weight as a percent of brain weight. Brain, adrenals, epididymides, heart, kidneys, liver, lung, ovaries, pituitary, testes, thyroid/parathyroid, and uterus.*

Liver

In males dosed at  $\geq 65$  mg/kg, there was a dose-related increase in liver weight (36-54%  $\uparrow$ ; liver/brain wt ratio). A similar increase was not observed in females. There were no corresponding microscopic findings.

The increase in liver weight is consistent with the increases in liver weight (16-22%  $\uparrow$ ; liver/body wt ratio) without corresponding microscopic findings or clinical chemistry changes (e.g., ALT or AST changes) in male mice dosed at  $\geq 65$  mg/kg in the 13-week study. The sponsor attributed the increase in weight to hepatocellular hypertrophy too slight to see microscopically that was the result of test article-related induction of enzymes within the hepatocytes.

Ovaries and Uterus

In females dosed at  $\geq 100$  mg/kg, there was a decrease in the weight of the ovaries (40-52%  $\downarrow$ ; ovaries/brain wt ratio). There was also a significant dose-related decrease in the weight of the uterus (91-94%  $\downarrow$ ) in females dosed at  $\geq 25$  mg/kg. The decrease in uterine weight correlated with atrophy of the uterus and a decrease in the incidence and severity of cystic endometrial hyperplasia compared to controls.

Male: Organ Weights			
Dose (mg/kg)	N	Liver	
		Grams	% Br Wt
0	15	2.18	4.37
12.5	13	1.99	4.13
65	14	2.85	5.88
100	11	3.16	6.66

Female: Organ Weights					
Dose (mg/kg)	N	Ovaries		Uterus	
		Grams	% Br Wt	Grams	% Br Wt
0	14	0.212	0.444	1.46	3.08
25	20	0.311	0.674	0.14	0.28
100	19	0.105	0.214	0.11	0.22
300/200/125	9	0.14	0.268	0.09	0.18

Shaded values indicate  $p < 0.05$  compared to control

**Gross Pathology**

Relative to controls, there was treatment-related decrease in the incidence and severity of the observation of enlarged uterus with cervix in females dosed at  $\geq 25$  mg/kg. This corresponded to the decrease in the incidence of uterine cystic endometrial hyperplasia observed microscopically.

**Macroscopic Findings (Sponsor's Table)**

Tissue Observation	Severity	0 mg/kg		25 mg/kg		100 mg/kg		300/200/125 mg/kg	
		DOS	SNC	DOS	SNC	DOS	SNC	DOS	SNC
Number of Animals Examined		46	14	40	20	41	19	51	9
uterus with cervix enlarged		15	11	0	1	1	0	1	1
	- mild	6	5	0	1	0	0	1	1
	- moderate	8	6	0	0	1	0	0	0
	- severe	1	0	0	0	0	0	0	0

**Histopathology**

*No peer review of neoplastic/non-neoplastic findings was conducted.*

**Neoplastic**

There were no statistically significant increases found by trend test comparison or pair-wise analysis in the incidence of any tumor type in any mifepristone-treated group compared to the control groups in the sponsor's analysis or in the independent FDA statistical analysis.

**Non-Neoplastic**

In females dosed at  $\geq 25$  mg/kg, there was a dose-related increase in the incidence and severity of uterine atrophy. The atrophy was characterized by smaller horns in cross section, attributable to lesser smooth muscle, stromal, and epithelial components. There was also a decrease in the incidence and severity of cystic endometrial hyperplasia across mifepristone-treated female groups compared to controls.

Tissue Observation	Severity	0 mg/kg		25 mg/kg		100 mg/kg		300/200/125 mg/kg	
		DOS	SNC	DOS	SNC	DOS	SNC	DOS	SNC
Number of Animals Examined		46	14	40	20	41	19	51	9
atrophy		0	0	15	2	17	8	50	9
	- minimal	0	0	5	0	0	1	1	0
	- mild	0	0	7	2	1	4	6	5
	- moderate	0	0	3	0	10	1	12	1
	- severe	0	0	0	0	6	2	31	3
hyperplasia, cystic endometrial		27	13	5	7	6	8	4	2
	- minimal	10	5	5	7	6	8	4	2
	- mild	15	5	0	0	0	0	0	0
	- moderate	2	3	0	0	0	0	0	0

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**Toxicokinetics**

*Predose, and at 1,2,4,8, 12, and 24 hours postdose on Days 1 and 177 (Week 26).*

Mifepristone (C-1073) was metabolized into RU42633, RU42698, and RU42848 with detection of metabolite plasma concentrations within one hour of mifepristone administration. Exposure ( $C_{max}$  and  $AUC_{0-24}$ ) increased with dose for all four analytes.

Systemic exposure to the parent and the 3 metabolites changed with repeat dosing. In males and females, mifepristone systemic exposures ( $AUC$  and  $C_{max}$ ) at Week 26 were generally lower or the same as those on Day 1. RU42633 and RU42698 exposures generally decreased with repeat dosing, RU42848 exposures generally increased or remained the same.

After 26 weeks of dosing, males administered 12.5, 65, and 125 mg/kg mifepristone achieved exposures of ~0.04X, 0.4X, and 0.6X the MRHD of 1200 mg/day (AUC basis; parent and 3 metabolites), respectively. Females administered 25, 100, and 300 mg/kg mifepristone achieved exposures of ~0.1X, 0.5X, and 2X the MRHD of 1200 mg/day (AUC basis; parent and 3 metabolites), respectively. Given that the dose of the female high dose group was decreased to 125 mg/kg from Week 54 onward, the AUC value of the mid dose group (100 mg/kg) likely approximates exposure at the high dose. Therefore, exposure (parent and 3 active metabolites) in all three dose groups did not exceed clinical exposure.

#### Male TK Parameters (Sponsor's Table)

Analyte	Parameter	12.5 mg/kg		65 mg/kg		125 mg/kg	
		Day 1	Week 26	Day 1	Week 26	Day 1	Week 26
C-1073	C <sub>max</sub> (ng/mL)	409.5	357.1	2949.8	2405.9	8906.7	4361.4
	T <sub>max</sub> (hour)	1.0	1.0	1.0	2.0	1.0	1.0
	AUC <sub>0-24</sub> (ng·h/mL)	984.5	1039.6	13437.5	12325.0	40022.7	22682.8
RU 42633	C <sub>max</sub> (ng/mL)	336.7	198.2	1426.8	889.3	3825.2	1653.6
	T <sub>max</sub> (hour)	1.0	1.0	2.0	2.0	1.0	1.0
	AUC <sub>0-24</sub> (ng·h/mL)	697.7	545.5	7019.3	4711.7	16238.1	8328.9
RU 42698	C <sub>max</sub> (ng/mL)	353.9	261.3	1792.4	1057.5	3529.7	1955.6
	T <sub>max</sub> (hour)	1.0	1.0	1.0	2.0	1.0	2.0
	AUC <sub>0-24</sub> (ng·h/mL)	833.7	768.0	9448.4	6710.7	22467.6	12877.9
RU 42848	C <sub>max</sub> (ng/mL)	649.4	653.8	2362.8	2345.6	3086.9	3593.2
	T <sub>max</sub> (hour)	1.0	1.0	2.0	2.0	4.0	1.0
	AUC <sub>0-24</sub> (ng·h/mL)	2323.7	2399.3	14044.8	18697.2	32351.3	29933.1

#### Female TK Parameters (Sponsor's Table)

Analyte	Parameter	25 mg/kg		100 mg/kg		300 mg/kg	
		Day 1	Week 26	Day 1	Week 26	Day 1	Week 26
C-1073	C <sub>max</sub> (ng/mL)	1317.6	1204.3	6875.0	4836.3	11350.8	10150.7
	T <sub>max</sub> (hour)	1.0	1.0	1.0	2.0	1.0	2.0
	AUC <sub>0-24</sub> (ng·h/mL)	3462.8	2990.3	34197.2	19798.0	82731.8	90427.2
RU 42633	C <sub>max</sub> (ng/mL)	945.3	709.2	3703.9	2002.1	4795.0	3786.1
	T <sub>max</sub> (hour)	1.0	1.0	1.0	2.0	1.0	2.0
	AUC <sub>0-24</sub> (ng·h/mL)	2519.5	1659.1	19082.7	7996.8	40265.0	32462.0
RU 42698	C <sub>max</sub> (ng/mL)	1098.4	1008.0	3467.6	2781.9	3712.1	8779.5
	T <sub>max</sub> (hour)	1.0	1.0	2.0	2.0	1.0	4.0
	AUC <sub>0-24</sub> (ng·h/mL)	3008.7	2840.8	22987.6	14342.2	48645.4	76206.0
RU 42848	C <sub>max</sub> (ng/mL)	1477.6	1322.3	2809.0	3033.7	4809.9	6563.6
	T <sub>max</sub> (hour)	1.0	1.0	2.0	2.0	12.0	4.0
	AUC <sub>0-24</sub> (ng·h/mL)	5660.8	5732.4	29400.8	22793.9	80515.5	86551.6

#### Dosing Solution Analysis

The homogeneity analyses results were within the expected range of <10% relative standard deviation. All the concentration verification samples were within the expected range of ±15% of the nominal concentration except the 1.25 mg/mL formulation sample in Week 16 (143% of nominal) and Week 60 (144.8%). Additionally, the 6.5 mg/mL formulation sample was 128.9% of the nominal value in Week 60. However, these higher than expected values were likely a result of a sampling error as the other samples analyzed at this level were within the expected range. Thus, the sporadic deviations did not affect the integrity of the study over the 2-year dosing period.

## 9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were conducted in support of this application. The use of Korlym<sup>®</sup> is contraindicated in women who are pregnant or may become pregnant because of the possibility of pregnancy termination due to mifepristone's potent anti-progestational effect.

The sponsor is relying on the fertility data in the approved Mifeprex<sup>®</sup> (mifepristone) label under its 505(b)(2) application. Due to drug-related disruption of the estrus cycle, even at doses as low as 0.3 mg/kg, studies designed to assess the effects on fertility during drug administration were precluded. However, three studies in rats were conducted to determine the residual effects on reproductive function following termination of drug exposure as described in the approved Mifeprex<sup>®</sup> (mifepristone) label. For the MRHD of 1200 mg/day, estimated safety margins were calculated using body surface area exposure (mg/m<sup>2</sup>) based on the body weight of 70 kg (634 mg/m<sup>2</sup>).

According to the approved label for Mifeprex<sup>®</sup> (mifepristone):

In rats, administration of the lowest oral dose of 0.3 mg/kg/day [1.8 mg/m<sup>2</sup>/day; <1X the MRHD; mg/m<sup>2</sup> basis] caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effect on reproductive performance was observed. In a neonatal exposure study in rats, the administration of a subcutaneous dose of mifepristone up to 100 mg/kg [600 mg/m<sup>2</sup>/day; ~1X the MRHD; mg/m<sup>2</sup> basis] on the first day after birth had no adverse effect on future reproductive function in males or females. The onset of puberty was observed to be slightly premature in female rats neonatally exposed to mifepristone. In a separate study in rats, oviduct and ovary malformations in female rats, delayed male puberty, deficient male sexual behavior, reduced testicular size, and lowered ejaculation frequency were noted after exposure to mifepristone (1 mg every other day) as neonates.

Teratology studies in mice, rats and rabbits discussed Mifeprex<sup>®</sup> label were conducted at doses with exposures (estimated using body surface area) significantly lower than estimated exposure at the MRHD. Skull deformities detected in rabbit studies were attributed to the mechanical effects of uterine contractions resulting from decreased progesterone levels. No teratogenic effects of mifepristone were observed in rats or mice.

## 11 Integrated Summary and Safety Evaluation

This is a 505(b)(2) application for the immediate release formulation of mifepristone (Korlym<sup>®</sup>) to treat the clinical and metabolic effects of hypercortisolism in patients with endogenous Cushing's syndrome. The listed drug is Mifeprex<sup>®</sup> (mifepristone) tablets (200 mg), which was approved under NDA 20687 (Danco Laboratories/Population Council) for the termination of pregnancy; single oral dose of three 200 mg Mifeprex<sup>®</sup> tablets.

Given that mifepristone (Mifeprex<sup>®</sup>) was approved for an acute indication, at the request of the Agency, the sponsor conducted a 12-month toxicology study in dogs and 2-year carcinogenicity studies in the mouse and rat to support the proposed chronic indication for the treatment of Cushing's syndrome. The Sponsor also conducted two *in vitro* hERG studies, pharmacokinetic 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. The sponsor is referencing the

nonclinical genotoxicity and fertility data in the Mifeprex<sup>®</sup> label (Danco Laboratories/Population Council) as allowed under this 505(b)(2) application.

Exposure at the proposed maximum recommended human dose (MRHD) of 1200 mg/day was established in healthy male volunteers administered mifepristone (1200 mg/day) once daily for 7 days (Study C-1 073-19). Safety margins were based on the combined exposure of mifepristone and its three major, pharmacologically active metabolites (RU42633, RU42848, and RU42698) at 1200 mg/day ( $AUC_{0-24}=122 \mu\text{g}\cdot\text{h/mL}$ ).

## Pharmacology

Mifepristone is a potent progesterone and glucocorticoid receptor type II (GRII) antagonist with some moderate anti-androgen properties as well. Three major metabolites of mifepristone (each >10% of total drug-related exposure) identified in humans and nonclinical species also possess anti-progestational and anti-glucocorticoid properties (Deraedt et al., 1985). As an anti-glucocorticoid, mifepristone acts at the cellular level to prevent the biological effects of cortisol by competing with cortisol's binding to the GRII, centrally and peripherally. The sponsor is proposing to use mifepristone to treat the clinical and metabolic manifestations of hypercortisolism in patients with endogenous Cushing's syndrome due to its ability to compete with cortisol for the binding to the GRII.

The safety pharmacology assessment was limited to two studies to assess the effects of mifepristone and its three major metabolites on the potassium selective  $I_{Kr}$  (tail) current (hERG studies). An initial hERG study (T-013; June 2005) found that mifepristone did not significantly effect hERG tail current density at mifepristone concentrations (3-140  $\mu\text{g/mL}$ ;  $\sim 7\text{-}326 \mu\text{M}$ ) ranging from the  $C_{max}$  at the MRHD of 1200 mg/day (7 days;  $C_{max}=3.1 \mu\text{g/mL}$ ) in healthy subjects to a concentration at least 30 times higher. A second hERG study (T-025; January 2011) using a different protocol was conducted to evaluate the effects of the three active metabolites RU42633 (up to 30  $\mu\text{M}$ ; 13  $\mu\text{g/mL}$ ), RU42698 (up to 30  $\mu\text{M}$ ; 13  $\mu\text{g/mL}$ ), and RU42848 (up to 3  $\mu\text{M}$ ; 1  $\mu\text{g/mL}$ ) as well as mifepristone (up to 10  $\mu\text{M}$ ; 4  $\mu\text{g/mL}$ ). This study found that mifepristone ( $IC_{50}$  of >10  $\mu\text{M}$  [ $>4 \mu\text{g/mL}$ ]) and its metabolites RU42633 ( $IC_{50}$  of 15  $\mu\text{M}$  [4  $\mu\text{g/mL}$ ]), RU42698 ( $IC_{50}$  of 26  $\mu\text{M}$  [12  $\mu\text{g/mL}$ ]), and RU42848 ( $IC_{50}$  of >3  $\mu\text{M}$  [1  $\mu\text{g/mL}$ ]) caused a concentration-related inhibition hERG mediated  $I_{Kr}$  current. It is unclear as to what accounts for the different findings of the two studies. Although the  $IC_{50}$  concentrations established for mifepristone ( $>4 \mu\text{g/mL}$ ;  $\sim 1\text{X}$  of the clinical  $C_{max}$  of 3  $\mu\text{g/mL}$ ), RU42633 (4  $\mu\text{g/mL}$ ;  $\sim 2\text{X}$  of the clinical  $C_{max}$  of 1.7  $\mu\text{g/mL}$ ), RU42698 (12  $\mu\text{g/mL}$ ;  $\sim 17\text{X}$  of the clinical  $C_{max}$  of 0.7  $\mu\text{g/mL}$ ), and RU42848 ( $>1 \mu\text{g/mL}$ ;  $\sim 1\text{X}$  of the clinical  $C_{max}$  of 1.3  $\mu\text{g/mL}$ ) were generally higher than those at the estimated peak plasma concentrations at the MRHD (1200 mg/day), there was a clear dose-related inhibition for each. Moreover, in the chronic dog study, there was a slight QTc prolongation (6-8 msec) postdose in the high dose group (60/40 mg/kg;  $\sim 1\text{X}$  MRHD of 1200 mg/kg; AUC basis) at Week 52. Given the biological relevance of the nonclinical findings, the sponsor conducted a clinical thorough QT study in which healthy male subjects were dosed for 14 days with 1800 mg mifepristone (supratherapeutic), 600 mg mifepristone, or placebo. The study was considered to be inconclusive by the Agency's Interdisciplinary Review Team as the assay sensitivity was not established.

## PK/ADME

Mifepristone is metabolized into the metabolites RU42633, RU42848, and RU42698 that subsequently undergo further hydroxylation or acetylation (Agarwai, 1996; Jang et al., 1996). Measureable amount of all three pharmacologically active metabolites, each greater

than 10 percent of total drug-related exposure, were formed in all four species (mouse, rat, dog, and monkey) studied. In the pivotal subchronic and chronic studies, systemic exposure of mifepristone and its three metabolites combined did not exceed clinical exposure at the MRHD of 1200 mg/day (121  $\mu\text{g}\cdot\text{h}/\text{mL}$ ; based on AUC) in the mouse (up to 26 weeks), rat (up to 26 weeks), or dog (up to 26 weeks). Higher exposures were not achievable due to the toxicity of the drug. Moreover, as the dose was increased there was a lack of dose-proportionality for mifepristone and its metabolites such that an increase in dose did not significantly increase exposure. This was also observed clinically.

Although the sponsor did not conduct *in vivo* distribution studies, studies in the published literature established that orally administered mifepristone is rapidly and widely distributed throughout the body including the kidney, liver, adipose tissue, endocrine organs, reproductive organs, and lung. Levels were also detectable in the brain up to 24 hours postdose, although they were lower than those observed in the plasma. The sponsor demonstrated that mifepristone is highly bound to plasma proteins in the rat, monkey, and human. The active metabolites are also highly protein bound in human plasma; the binding of the metabolites was not assessed in nonclinical species.

CYP3A4 is considered to be the enzyme primarily responsible for the demethylation and hydroxylation of mifepristone (Jang et al., 1996), although CYP2B and CYP2C may also contribute to the demethylation process (Chasserot-Golaz and Beck, 1992). Interestingly, mifepristone itself has been shown to inhibit (He et al., 1999) as well as induce CYP3A4/CYP3A (Cheesman and Reilly, 1998; Kocarek et al., 1995; Williams et al., 1997). However, drug levels would be expected to increase over time despite the induction of CYP3A4/CYP3A as the enzymes become partially inactivated at liver drug concentrations.

In addition to its effects on CYP3A4/CYP3A, mifepristone appears to affect the activity of additional CYP450 enzymes (e.g., CYP2A6, CYP2C8, CYP2C9, and CYP2C19). Mifepristone also was found to inhibit the transport of drugs via P-glycoprotein (P-gp) (Woodland et al., 2003) and efflux and uptake transporters. Clinical studies were conducted by the sponsor to evaluate the effects of mifepristone on CYP2C8/9 and CYP3A and the transporter P-gp to assess possible drug-drug interactions.

### **General Toxicology**

The sponsor conducted repeat dose studies in the mouse (up to 3 months), rat (up to 3 months), dog (up to 12 months) in support of this application. Pharmacokinetic studies in the dog and monkey established that higher exposure could be achieved in the dog, and that oral dosing in dogs resulted in higher plasma concentrations than did dosing by subcutaneous injection. Thus, the chronic toxicity study for this program was conducted in dogs using oral administration.

The combined systemic exposure of mifepristone and its three active metabolites did not exceed clinical exposure ( $\leq 1\text{X}$  MRHD of 1200 mg/day; AUC basis) in the pivotal subchronic and chronic studies due to the toxicity of the drug. This was most evident in the dog where exposures slightly exceeding the estimated clinical exposure at the MRHD ( $\geq 2\text{X}$  MRHD; AUC basis) caused moribundity. Thus, the nonclinical evaluation is limited by the low exposure achieved.

The treatment-related effects identified in all species were generally attributable to the pharmacodynamic activity (i.e., anti-glucocorticoid, anti-progestin, and anti-androgen).

However, adverse findings in the liver and retinal effects were not clearly related to the pharmacodynamic activity of mifepristone.

### Endocrine Organs

Treatment-related effects in the pituitary, adrenal gland and thyroid are attributable to perturbations of the HPA axis as the result of mifepristone's central anti-glucocorticoid activity. Although these anti-glucocorticoid effects occurred in the mouse, rat and dog, the rat appears to be the most sensitive with effects occurring at exposures considerably less than clinical exposure at the MRHD. The hypertrophic effects on pituitary and adrenal glands are attributable to the blockade of the cortisol's negative feedback at the central GR1s and subsequent increases in ACTH and cortisol levels, although ACTH and cortisol levels were not assessed in the nonclinical studies. Given the elevated plasma cortisol and ACTH levels of patients with Cushing's syndrome, the clinical relevance is expected to be minimal.

An increase in thyroid weight occurred in the mouse ( $\geq 500$  mg/kg; 4-week study; no TK data), rat (125 mg/kg; 13-week study;  $\sim 0.5X$  MRHD of 1200 mg/day; AUC basis), and dog ( $\geq 25$  mg/kg; 12-month study;  $\sim 1X$  MRHD of 1200 mg/day; AUC basis). In the 2-year rat study, thyroid enlargement was associated with a dose-related increase in incidence and severity of follicular cell hypertrophy and hyperplasia mainly in the mid and high dose groups ( $\leq 1X$  MRHD; AUC basis). Moreover, in the high dose female rats in the 2-year study, treatment-related follicular cell tumors developed ( $\sim 1X$  MRHD of 1200 mg/day; AUC basis). The lack of thyroid findings in the 2-year mouse study may be due to the lower doses administered (up to 300/200/125 mg/kg compared to 500 mg/kg [4-week study]) as a result of tolerability. Clinically, chronic mifepristone treatment has caused elevations in serum TSH and transient decreases in T4 (hypothyroidism) in Cushing's patients (Study 400 and Study 415), as well as in patients with meningioma (Heikinheimo et al., 1997).

### Reproductive Organ Effects

Effects attributable to the anti-progesterone activity of mifepristone occurred in the mouse, rat, and dog at exposures that are considerably less than clinical exposure at the MRHD. Uterine effects in the mouse and rat included a reduction in weight, atrophy, and dilatation of uterine gland. Although there was a treatment-related increase in diffuse squamous cell hyperplasia of cervical epithelium and vaginal epithelium in the mouse at doses as low as 12.5 mg/kg (no TK data) in the subchronic study, no neoplastic findings in the female reproductive organs were identified in the 2-year mouse or rat bioassay at doses that achieved exposures near clinical exposure ( $\sim 1X$  MRHD of 1200 mg/day; AUC basis). In fact, there was actually a decrease in the incidence and severity of cystic endometrial hyperplasia at doses of  $\geq 25$  mg/kg ( $< 1X$  MRHD of 1200 mg/day) in the 2-year mouse bioassay. Moreover, mammary gland ectasia and thickening of the subcutaneous tissue observed in rats ( $\geq 5$  mg/kg) at exposure less than clinical exposure at the MRHD in the subchronic study did not result in neoplastic changes in the chronic 2-year study. However, because dosing was limited by toxicity, the lack of neoplastic findings is lessened by the fact that drug exposure in both rats and mice ( $\leq 1X$  MRHD of 1200 mg/day; AUC basis) did not exceed clinical exposure at the MRHD. In the pivotal 12-month dog study, effects were limited to the absent corpora lutea in the ovaries and uterine anestrus. Overall, the treatment-related female reproductive organ findings in nonclinical species are consistent with those observed clinically (Eisinger et al., 2005; Koide, 1998; Newfield et al., 2001; Spitz, 2003; Spitz et al., 2005; Williams et al., 1997).

Adverse effects on the male reproductive system in the rat and dog at exposures below clinical exposure were attributable to the anti-androgenic effects of mifepristone; no treatment-related changes were noted in mice. In chronically treated dogs ( $\geq 25$  mg/kg;  $93 \mu\text{g}\cdot\text{h}/\text{mL}$ ;  $<1\text{X}$  MRHD; AUC basis), treatment-related effects occurred in the prostate, testes, and epididymides. A decrease in testes weight was associated with testicular/seminiferous tubule degeneration/atrophy and a decrease in developing spermatids within the seminiferous tubules. There were also reduced numbers of mature spermatocytes within tubules of the epididymides suggesting that mifepristone affects sperm production at clinically relevant doses. In the prostate, mild to severe atrophy was associated with a decrease in secretory tubules/alveoli. No treatment-related changes in serum testosterone or dihydroxytestosterone were associated with these changes. Treatment-related effects in the male reproductive organs of the rat (epididymis, seminal vesicles, and prostate) were also compatible with those associated with androgen levels reduction or receptor blockage treatment-related effects. In the chronically treated rat ( $\geq 25$  mg/kg;  $19 \mu\text{g}\cdot\text{h}/\text{mL}$ ;  $<1\text{X}$  MRHD; AUC basis), in addition to atrophy of the epididymis, seminal vesicles, and prostate, there was a reduction in luminal secretion in the prostate and seminal vesicle, as well as oligospermia. In the 13-week subchronic rat study, there were only prostate effects (decreased weight and inflammation) indicating that the effects are time dependent. The reversibility of these adverse pharmacodynamic effects was not established.

### Lungs

Subacute lung inflammation in the chronic dog study and pulmonary histiocytosis in the 2-year rat bioassay at exposures less than or equal to the estimated maximum clinical exposure appear to be treatment-related. These effects are also likely due to blockade of the GR $\beta$ . Clinically, mifepristone has been associated with development of pneumonia (Johanssen and Allolio, 2007).

### Liver

The liver appears to be a target organ of toxicity. Increased liver weight occurred in the mouse, rat, and dog at exposures less than clinical exposure ( $<1\text{X}$  MRHD; AUC basis). Increased liver weight and corresponding centrilobular hypertrophy ( $<1\text{X}$  MRHD; AUC basis) in the subchronic rat study is possibly due to CYP3A induction. In the 2-year rat bioassay, findings of hepatocellular toxicity (i.e., single cell necrosis, multinucleated hepatocytes, basophilic cell foci, and increased pigmentation) were also noted ( $\leq 1\text{X}$  MRHD; AUC basis). Moreover, elevated ALT levels ( $\sim 2\text{-}11\text{X}$   $\uparrow$ ) and hepatocellular pigmentation occurred in the chronic dog study at exposure equal to or less than clinical exposure at 1200 mg/day. Based on the description provided, the hepatocellular pigmentation in the rat and dog chronic studies was possibly lipofuscin, although this was not confirmed by staining. In mice, while increased liver weight was noted at clinical exposure levels, hepatocellular toxicity ( $\uparrow$  liver weight, hypertrophy,  $\uparrow$  ALT, AST and bilirubin, and necrosis) occurred at doses where exposure likely exceeded clinical exposure ( $\geq 500$  mg/kg; no TK data provided; 1-month study). No significant increases in ALT have occurred in the clinical studies.

### Retinal Degeneration

In the 2-year rat study, treatment-related retinal atrophy developed in rats at doses achieving exposures comparable to those at the MRHD of 1200 mg/day. As early as Week 52, diffuse retinal degeneration was detected by slit lamp examination. Microscopic examination revealed retinal atrophy ranging from a decrease in photoreceptor cell bodies at the far periphery (minimal) to outer layer atrophy affecting a large part of the retina with

retinal/choroidal vascular anastomosis (severe). There was also a low incidence of chorioretinal atrophy in the subchronic 13-week rat study at 5 mg/kg (1 µg·h/mL; ~0.01X MRHD; AUC basis) and 125 mg/kg (48-57 µg·h/mL; ~0.5X MRHD of 1200 mg/day) with no retinal atrophy noted in the controls. However, no treatment-related observations were noted in the ophthalmoscopic examinations of the 2-year mouse study, 13-week mouse study, or the 1-year dog study indicating that the retinal atrophy is limited to the albino rat.

As the affected animals were distributed in various rows of the racks, disproportionate exposure to light was excluded as a causative factor for the retinal degeneration. However, this does not rule out the possibility that treatment caused an increased sensitivity to light. The ocular pathologist contracted by the sponsor suggested that mifepristone is affecting the “biologic systems that regulate the albino rodent-specific retinal atrophy phenomenon.” FDA ophthalmology reviewers commented that it is difficult to tell if these nonclinical findings present additional clinical risk beyond that known when glucocorticoids are perturbed in human subjects. The sponsor was asked by the Agency to conduct complete eye exams at entry and every six month for clinical studies longer than 6 weeks in duration. No treatment-related retinal atrophy has been in the clinical studies to date.

### **Genetic Toxicology**

Mifepristone was not mutagenic or clastogenic with or without metabolic activation in two *in vitro* assays (Ames and chromosome aberration) conducted by the sponsor. This is in agreement with the negative genotoxicity findings in the approved Mifeprex<sup>®</sup> (mifepristone) label.

### **Carcinogenicity**

The carcinogenic potential of mifepristone and its three metabolites were evaluated in 2-year bioassays in the mouse and rat. Exposures at the doses tested in both the rat and mouse did not exceed clinical exposure ( $\leq 1X$  MRHD) as dosing of mifepristone was limited by toxicity. Despite this limitation, the bioassays in rats and mice are considered an acceptable evaluation of carcinogenesis with mifepristone.

In the 2-year rat bioassay, there was an increase in hepatocellular adenomas, as well as follicular cell adenomas, carcinomas, and pooled adenomas/carcinomas in the high dose females (~1X MRHD; AUC basis). Hyperplasia (thyroid only) and hypertrophy were also noted in the liver and thyroid, mainly in the mid and high dose groups (both sexes;  $< 1X$  MRHD; AUC basis). The sponsor attributes the hepatocellular and follicular cell tumors to a rat-specific chronic induction of enzyme activity in the liver and subsequent increase in thyroid hormone metabolism resulting in thyroid hyperplasia and eventually neoplasia (Wu and Farrelly, 2006). However, the sponsor did not conduct any mechanistic studies to assess mifepristone's effect on thyroid function or hepatic enzyme activity. Plasma drug levels in females increased over time in the 2-year bioassay. Moreover, chronic mifepristone treatment caused elevations in serum TSH and transient decreases in T4 clinically (Heikinheimo et al., 1997). It is not clear to what extent the neoplastic findings might be related to liver enzyme induction. Thus, the relevance to humans cannot be excluded. Conflicting effects on mammary tumors were also noted in the 2-year rat bioassay. There was a marked decrease in fibroadenomas in all dose groups ( $\geq 5$  mg/kg), as well as an increase in adenomas/adenocarcinomas up to the mid dose (25 mg/kg). While the lack of a dose-response for the increase in adenomas/adenocarcinomas at the high dose may be attributable to a decrease in body weight at the high dose, the marked decrease in fibroadenomas appears to be consistent with the known pharmacology (i.e.,

progesterone antagonist) of the drug. As there were no treatment-related effects on mammary glands in the 2-year mouse bioassay, it seems unlikely that these conflicting findings indicate that mifepristone poses a significant mammary tumor risk in humans.

Mifepristone did not increase the incidence of any tumor in mice. Though, as exposures at the doses tested in mice did not exceed clinical exposure, the 'negative' tumor finding is tempered by the limited exposure achieved in the study.

### **Reproductive Toxicology**

The use of Korlym<sup>®</sup> is contraindicated in women who are pregnant or may become pregnant because of the possibility of pregnancy termination due to mifepristone's potent anti-progestational effect.

## **12 References**

- Agarwai,M.K. (1996). The antiglucocorticoid action of mifepristone. *Pharmacol Ther* 70, 183-213.
- Bertagna,X., Bertagna,C., Luton,J.P., Husson,J.M., and Girard,F. (1984). The new steroid analog RU 486 inhibits glucocorticoid action in man. *J Clin. Endocrinol. Metab.* 59, 25-28.
- Bertagna,X., Escourolle,H., Piquier,J.L., Coste,J., Raux-Demay,M.C., Perles,P., Silvestre,L., Luton,J.P., and Strauch,G. (1994). Administration of RU 486 for 8 days in normal volunteers: antiglucocorticoid effect with no evidence of peripheral cortisol deprivation. *J Clin. Endocrinol. Metab.* 78, 375-380.
- Cadepond,F., Ulmann,A., and Baulieu,E.E. (1997). RU486 (mifepristone): mechanisms of action and clinical uses. *Annu. Rev. Med.* 48, 129-156.
- Chasserot-Golaz,S. and Beck,G. (1992). How the potency of the steroid RU486 is related to P450 activities induced by dexamethasone and phenobarbital in rat hepatoma cells. *J Steroid Biochem Mol. Biol.* 41, 653-657.
- Cheesman,M.J. and Reilly,P.E. (1998). Differential inducibility of specific mRNA corresponding to five CYP3A isoforms in female rat liver by RU486 and food deprivation: comparison with protein abundance and enzymic activities. *Biochem Pharmacol* 56, 473-481.
- Cui,X., Thomas,A., Han,Y., Palamanda,J., Montgomery,D., White,R.E., Morrison,R.A., and Cheng,K.C. (2005). Quantitative PCR assay for cytochromes P450 2B and 3A induction in rat precision-cut liver slices: correlation study with induction in vivo. *J Pharmacol Toxicol. Methods* 52, 234-243.
- Deraedt,R., Bonnat,C., Busigny,M., Chatelet,P., Cousty,C., Mouren,M., Philibert,D., Pottier,J., and Salmon,J. (1985). Pharmacokinetics of RU 486. In *The Antiprogestin Steroid RU 486 and Human Fertility Control*, Etienne-Emile Baulieu and Sheldon J.Segal, eds. (New York: Plenum Press), pp. 103-122.
- Deraedt,R., Vannier,B., and Fournex,R. (2011). Toxicological Study on RU 486. In *The Antiprogestin Steroid RU 486 and Human Fertility Control*, E.E.Baulieu and S.J.Segal, eds. (New York: Plenum Press), pp. 123-126.

Eisinger,S.H., Bonfiglio,T., Fiscella,K., Meldrum,S., and Guzick,D.S. (2005). Twelve-month safety and efficacy of low-dose mifepristone for uterine myomas. *J Minim. Invasive. Gynecol.* 12, 227-233.

He,K., Woolf,T.F., and Hollenberg,P.F. (1999). Mechanism-based inactivation of cytochrome P-450-3A4 by mifepristone (RU486). *J Pharmacol Exp. Ther* 288, 791-797.

Healy,D.L., Chrousos,G.P., Schulte,H.M., Williams,R.F., Gold,P.W., Baulieu,E.E., and Hodgen,G.D. (1983). Pituitary and adrenal responses to the anti-progesterone and anti-glucocorticoid steroid RU 486 in primates. *J Clin. Endocrinol. Metab.* 57, 863-865.

Heikinheimo,O., Kontula,K., Croxatto,H., Spitz,I., Luukkainen,T., and Lahteenmaki,P. (1987a). Plasma concentrations and receptor binding of RU 486 and its metabolites in humans. *J Steroid Biochem* 26, 279-284.

Heikinheimo,O., Lahteenmaki,P.L., Koivunen,E., Shoupe,D., Croxatto,H., Luukkainen,T., and Lahteenmaki,P. (1987b). Metabolism and serum binding of RU 486 in women after various single doses. *Hum. Reprod.* 2, 379-385.

Heikinheimo,O., Pesonen,U., Huupponen,R., Koulu,M., and Lahteenmaki,P. (1994). Hepatic metabolism and distribution of mifepristone and its metabolites in rats. *Hum. Reprod.* 9 Suppl 1, 40-46.

Heikinheimo,O., Ranta,S., Grunberg,S., Lahteenmaki,P., and Spitz,I.M. (1997). Alterations in the pituitary-thyroid and pituitary-adrenal axes--consequences of long-term mifepristone treatment. *Metabolism* 46, 292-296.

Heikinheimo,O., Ranta,S., Grunberg,S., and Spitz,I.M. (2000). Alterations in sex steroids and gonadotropins in post-menopausal women subsequent to long-term mifepristone administration. *Steroids.* 65, 831-836.

Hill,N.C., Selinger,M., Ferguson,J., and Mackenzie,I.Z. (1991). Transplacental passage of mifepristone and its influence on maternal and fetal steroid concentrations in the second trimester of pregnancy. *Hum. Reprod.* 6, 458-462.

Jackson,T.A., Richer,J.K., Bain,D.L., Takimoto,G.S., Tung,L., and Horwitz,K.B. (1997). The partial agonist activity of antagonist-occupied steroid receptors is controlled by a novel hinge domain-binding coactivator L7/SPA and the corepressors N-CoR or SMRT. *Mol. Endocrinol.* 11, 693-705.

Jang,G.R., Wrighton,S.A., and Benet,L.Z. (1996). Identification of CYP3A4 as the principal enzyme catalyzing mifepristone (RU 486) oxidation in human liver microsomes. *Biochem Pharmacol* 52, 753-761.

Jarukamjorn,K., Sakuma,T., Yamamoto,M., Ohara,A., and Nemoto,N. (2001). Sex-associated expression of mouse hepatic and renal CYP2B enzymes by glucocorticoid hormones. *Biochem Pharmacol* 62, 161-169.

Johanssen,S. and Allolio,B. (2007). Mifepristone (RU 486) in Cushing's syndrome. *Eur. J Endocrinol.* 157, 561-569.

Kawai,S., Nieman,L.K., Brandon,D.D., Udelsman,R., Loriaux,D.L., and Chrousos,G.P. (1987). Pharmacokinetic properties of the antigluccorticoid and antiprogesterone steroid RU 486 in man. *J Pharmacol Exp. Ther* 241, 401-406.

Kemppainen,J.A., Lane,M.V., Sar,M., and Wilson,E.M. (1992). Androgen receptor phosphorylation, turnover, nuclear transport, and transcriptional activation. Specificity for steroids and antihormones. *J Biol. Chem.* 267, 968-974.

Kocarek,T.A., Schuetz,E.G., Strom,S.C., Fisher,R.A., and Guzelian,P.S. (1995). Comparative analysis of cytochrome P4503A induction in primary cultures of rat, rabbit, and human hepatocytes. *Drug Metab Dispos* 23, 415-421.

Koide,S.S. (1998). Mifepristone. Auxiliary therapeutic use in cancer and related disorders. *J Reprod. Med.* 43, 551-560.

Lamberts,S.W., Koper,J.W., and de Jong,F.H. (1991). The endocrine effects of long-term treatment with mifepristone (RU 486). *J Clin. Endocrinol. Metab.* 73, 187-191.

Leonhardt,S.A. and Edwards,D.P. (2002). Mechanism of action of progesterone antagonists. *Exp. Biol. Med.* (Maywood. ) 227, 969-980.

Mahesh,R., Bhuvana,S., and Begum,V.M. (2009). Effect of Terminalia chebula aqueous extract on oxidative stress and antioxidant status in the liver and kidney of young and aged rats. *Cell Biochem Funct.* 27, 358-363.

Moguilewsky,M. and Philibert,D. (1985). Biochemical Profile of RU 486. In *The Antiprogesterin Steroid RU 486 and Human Fertility Control*, Etienne-Emile Baulieu and Sheldon J.Segal, eds. (New York: Plenum Press).

Moorthy,J.N. and Singhal,N. (2005). Facile and highly selective conversion of nitriles to amides via indirect acid-catalyzed hydration using TFA or AcOH-H<sub>2</sub>SO<sub>4</sub>. *J Org Chem.* 70, 1926-1929.

Morgan,B.P., Swick,A.G., Hargrove,D.M., LaFlamme,J.A., Moynihan,M.S., Carroll,R.S., Martin,K.A., Lee,E., Decosta,D., and Bordner,J. (2002). Discovery of potent, nonsteroidal, and highly selective glucocorticoid receptor antagonists. *J Med. Chem.* 45, 2417-2424.

Newfield,R.S., Spitz,I.M., Isacson,C., and New,M.I. (2001). Long-term mifepristone (RU486) therapy resulting in massive benign endometrial hyperplasia. *Clin Endocrinol. (Oxf.)* 54, 399-404.

Peeters,B.W., Tonnaer,J.A., Groen,M.B., Broekkamp,C.L., van der Voort,H.A., Schoonen,W.G., Smets,R.J., Vanderheyden,P.M., Gebhard,R., and Ruigt,G.S. (2004). Glucocorticoid receptor antagonists: new tools to investigate disorders characterized by cortisol hypersecretion. *Stress.* 7, 233-241.

Philibert,D. (1984). RU38486: An Original Multifaceted Antihormone *In Vivo*. In *Adrenal Steroid Antagonism*, Agarwal MJ, ed. (Gruyer, Berlin: pp. 77-101.

Philibert,D., Moguilewsky,M., Mary,I., Lecaque,D., Tournemine,C., Secchi,J., and Deraedt,R. (1985). Pharmacological Profile of RU 486 in Animals. In *The Antiprogesterin*

Steroid RU 486 and Human Fertility Control, E.E.Baulieu and S.J.Segal, eds. (New York: Plenum Press).

Sartor,O. and Cutler,G.B. (1996). Mifepristone: treatment of Cushing's syndrome. Clin. Obstet. Gynecol. 39, 506-510.

Schreiber,J.R., Hsueh,A.J., and Baulieu,E.E. (1983). Binding of the anti-progestin RU-486 to rat ovary steroid receptors. Contraception 28, 77-85.

Sitruk-Ware,R. and Spitz,I.M. (2003). Pharmacological properties of mifepristone: toxicology and safety in animal and human studies. Contraception. 68, 409-420.

Song,L.N., Coghlan,M., and Gelmann,E.P. (2004). Antiandrogen effects of mifepristone on coactivator and corepressor interactions with the androgen receptor. Mol. Endocrinol. 18, 70-85.

Spitz,I.M. (2003). Progesterone antagonists and progesterone receptor modulators. Expert Opin. Investig. Drugs 12, 1693-1707.

Spitz,I.M., Grunberg,S.M., Chabbert-Buffet,N., Lindenberg,T., Gelber,H., and Sitruk-Ware,R. (2005). Management of patients receiving long-term treatment with mifepristone. Fertil. Steril. 84, 1719-1726.

Spitz,I.M., Heikinheimo,O., and Wade,C.E. (1993). The divergent effect of RU 486 on adrenal function in the dog is related to differences in its pharmacokinetics. Acta Endocrinol. (Copenh. ) 128, 459-465.

Trubetsky,O., Marks,B., Zielinski,T., Yueh,M.F., and Raucy,J. (2005). A simultaneous assessment of CYP3A4 metabolism and induction in the DPX-2 cell line. AAPS. J 7, E6-13.

Wagner,B.L., Norris,J.D., Knotts,T.A., Weigel,N.L., and McDonnell,D.P. (1998). The nuclear corepressors NCoR and SMRT are key regulators of both ligand- and 8-bromo-cyclic AMP-dependent transcriptional activity of the human progesterone receptor. Mol. Cell Biol. 18, 1369-1378.

Wagner,B.L., Pollio,G., Giangrande,P., Webster,J.C., Breslin,M., Mais,D.E., Cook,C.E., Vedeckis,W.V., Cidlowski,J.A., and McDonnell,D.P. (1999). The novel progesterone receptor antagonists RTI 3021-012 and RTI 3021-022 exhibit complex glucocorticoid receptor antagonist activities: implications for the development of dissociated antiprogestins. Endocrinology 140, 1449-1458.

Williams,J.A., Chenery,R.J., Berkhout,T.A., and Hawksworth,G.M. (1997). Induction of cytochrome P4503A by the antigluocorticoid mifepristone and a novel hypocholesterolaemic drug. Drug Metab Dispos 25, 757-761.

Wolf,J.P., Chillik,C.F., Itskovitz,J., Weyman,D., Anderson,T.L., Ulmann,A., Baulieu,E.E., and Hodgen,G.D. (1988). Transplacental passage of a progesterone antagonist in monkeys. Am. J Obstet. Gynecol. 159, 238-242.

Woodland,C., Koren,G., and Ito,S. (2003). From bench to bedside: utilization of an in vitro model to predict potential drug-drug interactions in the kidney: the digoxin-mifepristone example. *J Clin. Pharmacol* 43, 743-750.

Wu,K.M. and Farrelly,J.G. (2006). Preclinical development of new drugs that enhance thyroid hormone metabolism and clearance: inadequacy of using rats as an animal model for predicting human risks in an IND and NDA. *Am. J Ther* 13, 141-144.

Wu,W.N., McKown,L.A., Moyer,M.D., Johannsen,T.B., and Takacs,A.R. (1999). In vitro metabolism of mifepristone (RU-486) in rat, monkey and human hepatic S9 fractions: identification of three new mifepristone metabolites. *Xenobiotica* 29, 1089-1100.

Zhang,X., Jeyakumar,M., Petukhov,S., and Bagchi,M.K. (1998). A nuclear receptor corepressor modulates transcriptional activity of antagonist-occupied steroid hormone receptor. *Mol. Endocrinol.* 12, 513-524.

Zhou,S.F. (2008). Drugs behave as substrates, inhibitors and inducers of human cytochrome P450 3A4. *Curr Drug Metab* 9, 310-322.

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PATRICIA M BRUNDAGE  
01/19/2012

TODD M BOURCIER  
01/20/2012  
Pharm/tox supports approval

**BIOPHARMACEUTICS REVIEW**  
**Office of New Drug Quality Assessment**

<b>Application No.:</b>	NDA 202-107		
<b>Submission Date:</b>	15 April 2011	<b>Reviewer:</b> Minerva Hughes, Ph.D.	
<b>Division:</b>	Division of Metabolism and Endocrinology Products	<b>Supervisor (Acting):</b> Angelica Dorantes, Ph.D.	
<b>Sponsor:</b>	Corcept Therapeutics		
<b>Trade Name:</b>	(b) (4) Tablets	<b>Date Assigned:</b>	20 April 2011
		<b>PDUFA Date:</b>	18 Feb 2011
		<b>GRMP Date:</b>	14 Jan 2012
<b>Generic Name:</b>	Mifepristone tablets	<b>Date of Review:</b>	23 Dec 2011
<b>Indication:</b>	Hypercortisolism in patients with Cushing's syndrome	<b>Type of Submission:</b> Original NDA 505(b)(2)	
<b>Formulation/strengths</b>	Tablet/ 300 mg		
<b>Route of Administration</b>	Oral		

**SUBMISSION:**

Corcept Therapeutics has submitted a 505(b)(2) NDA for the use of mifepristone in the treatment of the signs and symptoms of endogenous Cushing's syndrome. Mifepristone is a synthetic progesterone analog shown to inhibit cortisol receptor activity. The compound's aqueous solubility is pH dependent, with a sharp decline in solubility between pH 1.5 – 2.0. At pH values above 2.5, the solubility of mifepristone is less than 0.5 mg/mL. Reference was made to DMF (b) (4) for drug substance chemistry, manufacturing and controls information.

The drug product is a yellow, oval-shaped, film-coated, immediate release tablet containing 300 mg of active and the following excipients: silicified microcrystalline cellulose, sodium starch glycolate, hydroxylpropyl-cellulose, sodium lauryl sulfate, magnesium stearate, hypromellose, titanium dioxide, triacetin, D&C yellow 10 aluminum lake, polysorbate 80, and FD&C yellow 6 aluminum lake. The manufacture of mifepristone tablets utilized (b) (4) process steps.

**BIOPHARMACEUTIC INFORMATION:**

In support of approval, NDA 202-133 included the following biopharmaceutics information for review and evaluation:

- **Drug substance solubility data**
- **Study C-1073-22:** A phase 1, open-label, randomized three-way crossover study of the effects of formulation and dissolution rate on the pharmacokinetics of mifepristone following a single 300 mg dose of mifepristone in healthy volunteers.
- **Dissolution method development information and assay validation reports**
- **Batch analyses/stability data:** Batch analyses data were submitted for some clinical lots and three primary stability batches. Different dissolution methods were used throughout the clinical development program. Long-term stability data through 36 months for the supportive drug product lots and 18 months for registration lots were submitted in the initial NDA. Accelerated stability data through 6 months were also submitted.

**RECOMMENDATION:**

The following dissolution method and acceptance criterion are acceptable.

(b) (4) <b>SMA.COR.007 Dissolution Method</b>	
<b>Medium</b>	USP pH 1.8 KCl buffer
<b>Apparatus</b>	USP 2 (paddle)
<b>Assay Method</b>	Direct UV, (b) (4) wavelength
<b>Sampling time points</b>	15, 30, 45, 60
<b>Acceptance Criterion</b>	Q = (b) (4) at 30 minutes

From ONDQA-Biopharmaceutics' perspective, NDA 202-107 for (b) (4) (mifepristone) Tablets is recommended for approval; however, the following advice comment should be sent to the Applicant.

Please convey the additional advice comment below to the applicant.

- *Your proposed dissolution method (b) (4) SMA.COR.007 and acceptance criterion of  $Q = (b) (4)$  at 30 minutes is acceptable. We encourage you to update the analysis method from direct UV to HPLC post approval.* (b) (4)

**Minerva Hughes, Ph.D.**

Biopharmaceutics Reviewer, ONDQA

**Angelica Dorantes, Ph.D.**

Acting Biopharmaceutics Supervisor, ONDQA

cc: filed in DARRTS

## BIOPHARMACEUTICS REVIEW NOTES

### 1.0 INTRODUCTION

#### 1.1 REGULATORY HISTORY

NDA 202-107 was submitted on 15 April 2011, for the use of mifepristone tablets to treat hypercortisolism in patients with endogenous Cushing's syndrome. The drug was first approved in 2000 under NDA 20-687 for pregnancy termination (200 mg tablet). A pre-NDA meeting was held on 14 Sept 2010, under IND 76,480. The following Biopharmaceutics comment was conveyed:

1. Include a dissolution method report covering dissolution profile data collected during development (i.e., selection of equipment, medium, pH, assay, etc.) and validation of the proposed method. The use of at least twelve samples per testing conditions was recommended and the applicant was advised that dissolution ranges are based on the mean target  $\pm 10\%$ .

Additional Biopharmaceutics regulatory advice comments were not found in the IND record on file.

Despite the Agency's request, NDA 202-107 was submitted without the complete dissolution method development information requested. A Biopharmaceutics information request was forwarded to the applicant on 28 June 2011, for the additional dissolution method development information. The NDA Amendment of 20 July 2011, provided responses to the 28 June 2011 request.

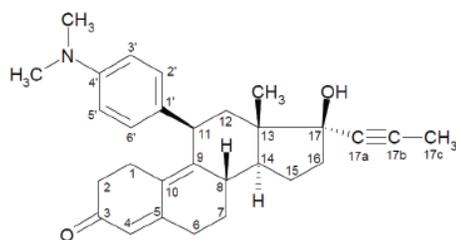
A teleconference was held with the Applicant on 26 Sept 2011, to discuss the Agency's concerns regarding their proposed dissolution method and changes implemented during the clinical development program. The Agency requested modifications to the method and additional elution profile data for lots on stability. Responses to the Agency's request were received on 19 Oct 2011, 21 Nov 2011 and 14 Dec 2011.

This review evaluates the biopharmaceutics information submitted in:

- Original Submission – 15 April 2011
- NDA Amendment – 20 July 2011
- Quality NDA Amendment – 19 Oct 2011
- Quality NDA Amendment – 21 Nov 2011
- Quality NDA Amendment – 14 Dec 2011

#### 1.2 GENERAL DRUG SUBSTANCE INFORMATION

Mifepristone is a selective antagonist of the type II glucocorticoid receptor and the progesterone receptor. The molecular structure and formulation is summarized below.



Formula: C<sub>29</sub>H<sub>35</sub>NO<sub>2</sub>

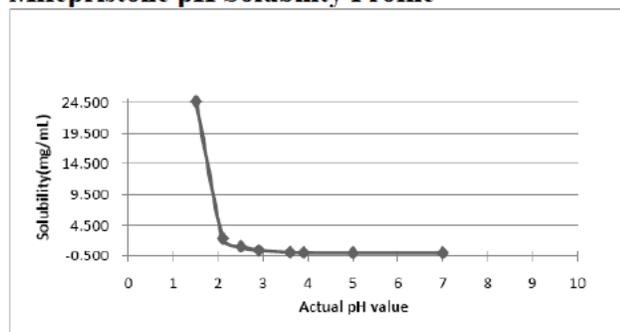
Mass: 429.58

General physiochemical properties were limited in the NDA and stated as follows.

- ClogP – 5.13 (b) (4)
- Aqueous solubility is pH dependent, with a sharp decline in solubility between pH 1.5 – 2.0.

The solubility profile is illustrated below.

### Mifepristone pH Solubility Profile



As submitted in the NDA.

Reference was made to DMF [REDACTED] (b) (4), for full details on the drug substance. The drug substance is [REDACTED] (b) (4).

### 1.3 GENERAL DRUG PRODUCT INFORMATION

The mifepristone drug product is formulated as an immediate release tablet containing 300 mg of the active ingredient, silicified microcrystalline cellulose, sodium starch glycolate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate, hypromellose, titanium dioxide, triacetin, D&C yellow 10 aluminum lake, polysorbate 80, and FD&C yellow 6 aluminum lake.

Tablets are produced by [REDACTED] (b) (4) steps. The proposed commercial batch size [REDACTED] (b) (4).

The proposed drug product will be packaged in two packaging configurations. A 28-count size is packaged in a (b) (4) high density polyethylene bottle with a child resistant closure [REDACTED] (b) (4). A 280-count size is packaged in a (b) (4) high density polyethylene bottle with a child resistant closure [REDACTED] (b) (4).

The composition information for the proposed commercial product is summarized in the table below.

### Drug Product Composition

Excipient	Amount per Tablet (mg)	% in Core Tablet	Function
(b) (4)			
Sodium Starch Glycolate			(b) (4)
Hydroxypropylcellulose			
Silicified Microcrystalline Cellulose			(b) (4)
Sodium Lauryl Sulfate			(b) (4)
(b) (4)			
Sodium Starch Glycolate			(b) (4)
Magnesium Stearate			
Total Core Tablet Weight:	(b) (4) (300 mg mifepristone)		
<i>Film Coating</i>			
			(b) (4)

As submitted in Table 1, NDA Section 3.2.P.2.

The composition of the different formulations used throughout clinical development is included in the Appendix of this report for reference. The proposed commercial formulation is different from earlier formulations. (b) (4) and the (b) (4) were changed. The proposed commercial formulation, however, was used in the pivotal clinical efficacy and safety study. Bioavailability data were also provided for the commercial formulation.

## 2.0 BIOPHARMACEUTICS QUALITY ASSESSMENT

This Biopharmaceutics review focused on the relationship between the physiochemical properties of the drug and proposed formulation with respect to in vivo performance (i.e., formulation pharmacokinetic (PK) studies) and the Applicant's strategy for assuring consistent in vivo product performance.

### 2.1 IN-VIVO STUDIES (FORMULATION ASSESSMENT)

A Caco-2 permeability study was completed (Study No. 5 CORCP1R1) using pindolol and atenolol as the high and low permeability controls. The mean apparent permeability Papp (A-B) value for mifepristone was numerically larger than that of pindolol, 28.9 (1.28) versus 19.4 (0.415) x 10<sup>-6</sup> cm/s, respectively. Based on these data and the low solubility of mifepristone, the Applicant concluded that the drug met the BCS Class 2 designation criteria. An in vitro/in vivo correlation (IVIVC) was not established for the mifepristone drug product.

Throughout clinical development, changes were made to the formulation that could impact product dissolution and clinical bioavailability. The different formulations were coded A1, A2, A3, B, C1 or E1, C2 or E2 in order of time on development (see appendix for details on formulation changes). Thus, the C2 or E2 formulation (terms used interchangeably in submission) referred to the intended final commercial formulation. A relative bioavailability study (Study C-1073-22) was completed to determine whether differences in dissolution rate or formulation composition had an effect on PK parameters.

Study C-1073-22 was a randomized 3-way crossover study in 15 healthy male subjects that compared the relative bioavailability of 3 mifepristone (300 mg) formulations after a single dose:

- Lot 8H21 (formulation C1/E1)
- Lot 8H23/8J16 (formulation C1/E1 (b) (4))
- Lot 5H14 – the first developed formulation, A1.

There was a two-week washout period between each dose of mifepristone. After each dose, blood samples were obtained over 96 hours to determine total plasma concentrations. Per the protocol, PK parameters calculated included  $T_{max}$ ,  $C_{max}$ ,  $AUC_{inf}$  and  $t_{1/2}$ . Equivalence comparisons of PK parameters around within-subject differences between treatments A versus B, A versus C and B versus C were performed using 90% confidence intervals (CIs) obtained from log-transformed PK parameters of mifepristone. An equivalence criterion of within 30% was defined. Less than a 30% increase or decrease in a PK parameter was concluded if the 90% CIs were contained within the interval (b) (4). The study results are summarized in the following two tables.

**Summary of PK Parameters**

Treatment		$T_{max}$ (h)	$C_{max}$ (ng/mL)	$AUC_{inf}$ (h*ng/mL)	Half-Life (h)
A	N	15	15	14	14
	Mean	4.50	1923	57552	29.74
	SD	12.05	950	32863	10.32
	CV%	267.7	49.4	57.1	34.7
B	N	15	15	15	15
	Mean	2.57	2057	63915	32.09
	SD	5.94	837	39820	16.93
	CV%	231.4	40.7	62.3	52.8
C	N	15	15	15	15
	Mean	1.43	2074	66292	32.28
	SD	0.78	841	44443	16.45
	CV%	54.1	40.6	67.0	51.0

As submitted in the NDA. A = Lot 5H14-old; B = Lot 8H21 – new, (b) (4); C = Lot 8H23 – new, (b) (4).

**Summary of Statistical Comparisons**

Parameter	A Geometric LS Means	B Geometric LS Means	C Geometric LS Means	Ratio	% Geometric Mean Ratio B/A	CI 90% Lower	CI 90% Upper
$C_{max}$	1659	1939	1902	B/A	1.17	0.85	1.61
				C/A	1.15	0.88	1.49
				C/B	0.98	0.76	1.27
$AUC_{inf}$	49482	55871	55691	B/A	1.13	0.97	1.32
				C/A	1.13	0.99	1.28
				C/B	1.00	0.88	1.12

As submitted in the NDA.  
A = Lot 5H14-old; B = Lot 8H21 – new, (b) (4); C = Lot 8H23 – new, (b) (4).

The Applicant concluded that the two new formulations, Lot 8H21 and 8H23 were bioequivalent and the observed differences between the old formulation and new formulation were not clinically significant.

**Reviewer’s Evaluation:** As per FDA Guidance “Bioavailability and Bioequivalence Studies for Orally Administered Drug Product, bioequivalence is demonstrated when the 90% CI for the mean ratios of  $C_{max}$  and  $AUC_{inf}$  fall within 0.80 – 1.25. The Applicant’s criterion (b) (4) does not comply with Agency standards. This review issue was discussed in detail with the NDA’s Clinical Pharmacology Reviewer Dr. Jee Eun Lee. Per these internal communications, FDA does not consider Study C1073-22 to be a pivotal bioequivalence study because the proposed commercial formulations were used in the pivotal clinical study. Therefore, Study C1073-22 is not required to

meet the 0.80-1.25 limit for approval. However, the Applicant's endpoint (b) (4) was not adequate to support the Applicant's claim of bioequivalence and lack of clinically meaningful differences. The Agency made no prior agreements with the Applicant to deviate from the current bioequivalence standard and does not agree that Study C1073-22 was adequately designed to demonstrate bioequivalence of the formulations (Refer to the ClinPharm Review for other comments on the study design and adequacy of the permeability data). Of note, none of the formulations exhibiting (b) (4) were used in the pivotal clinical study. Therefore, the Agency will only consider the in vitro performance of the drug products used in the pivotal clinical study as the target profile for assuring the quality of commercial lots. On the basis of the 0.80 – 1.25 CI limit, none of the formulations were bioequivalent; albeit, high inter-subject variability was noted and the limitations of the study design preclude any type of conclusive assessment.

## 2.2 DISSOLUTION METHOD DEVELOPMENT AND VALIDATION

Three (3) dissolution methods were developed for evaluating the in vitro performance of the drug product. The following table summarizes the method parameters for the different methods.

Method Parameter	(b) (4)	(b) (4) SMA COR.007	(b) (4)
Medium		pH 1.8 USP KCl buffer	
Medium Volume		900 mL	
Apparatus		USP 2	
Stirring Rate		50 rpm	
Sample Time points		15, 20, 30, 45, 60 minutes	
Analysis Method		Direct UV	

1 (b) (4)

The initial submission dated 15 Apr 2011, requested approval of the (b) (4) dissolution method with a proposed specification of:

(b) (4)

To allow for a complete review and evaluation of the method, the Agency requested, as part of the 74-day letter, the dissolution method development report, which was submitted on 20 Jul 2011.

(b) (4)

(b) (4)

**(b) (4) Method SMA.COR.007 Method Validation and Specification (19 Oct 2011, 21 Nov 2011, and 14 Dec 2011 NDA Amendments)**

- A dissolution method development report was not prepared for (b) (4) Method SMA.COR.007. A summary of the experimental work and rationale was summarized in the 14 Dec 2011 NDA amendment.

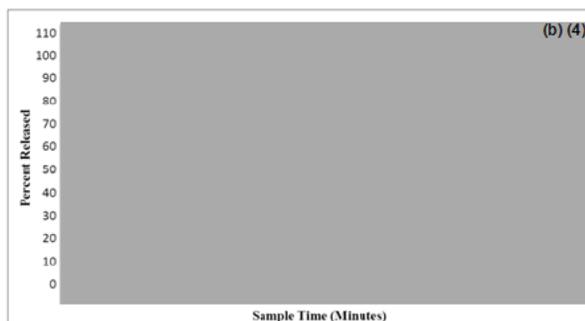
**Apparatus**

- The USP II apparatus was maintained from a previous method. The Applicant stated that the apparatus is commonly used for dosage forms and since no issues were noted with the paddle apparatus, it was utilized without further development. *(Reviewer's note: A USP II paddle apparatus is recommended in the FDA Dissolution Database for mifepristone tablets (USP II, 75 rpm, 0.01N HCl). Therefore, this apparatus is a reasonable starting point for the Applicant's product).*

**Medium Selection/Paddle Speed**

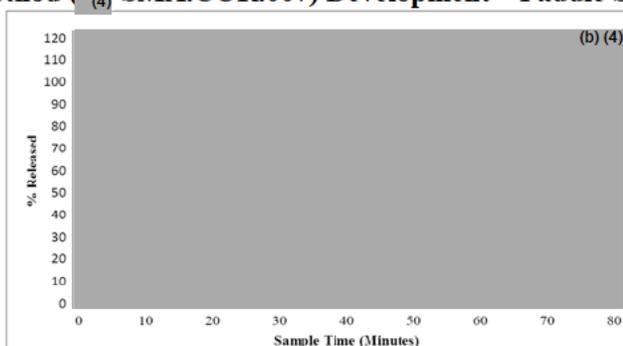
- Additional method development was completed because of changes to the drug product formulation. The new formulation rapidly dissolved when using the previous method (0.1 N HCl) and a desired two-point specification was not possible. An increase in pH was expected to slow the dissolution rate. Media at pH 1.8, 2.0, and 2.2 were tested using sample from Lot 040413A. Samples were tested using either a paddle speed of 50 rpm or 75 rpm. The data are illustrated in the figure below.

**Dissolution Method (b) (4) SMA.COR.007) Development – pH and Paddle Speed (Lot 040413A)**



As the pH increased, the dissolution rate slowed. At pH 2.2, the dissolution was not complete after 75 minutes. Also, the dissolution rate was faster at higher paddle speeds. A second study on the effects of paddle speed using lot 5K03 did not show a significant difference in dissolution rate between the two different paddle speeds.

**Dissolution Method (b) (4) SMA.COR.007) Development – Paddle Speed (Lot 5K03)**



Based on the data, USP pH 1.8 buffer was selected at a paddle speed of 50 rpm. *(Reviewer's note: This method was not developed at the time the commercial formulation was implemented. The observed faster dissolution rate for the commercial product using this method is what prompted another revision of the method.)*

- Solubility data were provided to demonstrate that sink conditions (at least 3X the solubility limit) were maintained using the USP pH 1.8 buffer. At an initial pH of 1.8, the solubility of mifepristone was 2.38 mg/mL. The addition of mifepristone slightly increased the pH of the solution to pH 2.1. *(Reviewer's note: The tablet strength of 300 mg is below 3X the solubility limit.)*

**Sampling Time and Specification Justification**

- The Applicant proposed an acceptance criterion of NLT Q (b) (4) at 30 minutes for the (b) (4) Method SMA.COR.007. The ~18 month stability data for the registration stability lots were tested using both the SMA.COR.007 and (b) (4) to bridge back to the initial method. The proposed specification was based on an analysis of the available release and stability data using method SMA.COR.007. At 30 minutes, the average mifepristone released was 97% with an RSD of 4.2% and individual tablet release ranges were from 85 – 109%. (b) (4)

(b) (4) The 30 minute time point and Q (b) (4) was selected (see Appendix for the supportive dissolution data).

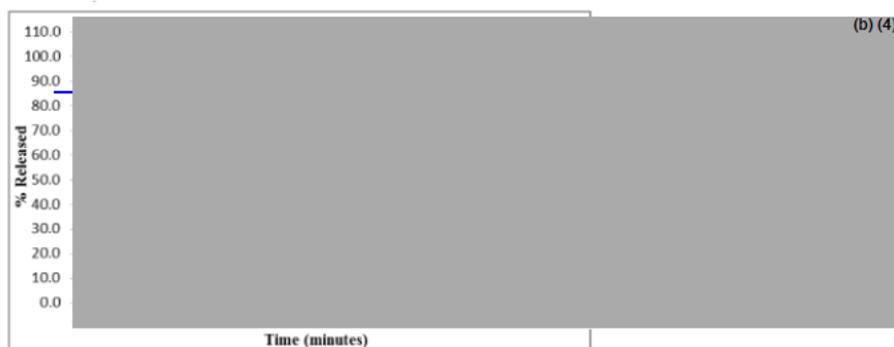
**Method Validation**

- The assay method used direct UV analysis. The methodology was continued from the previous method. The absorption spectrum was evaluated at pH 1.4, 1.8 and 2.2 to ensure that the proper wavelength was selected for analysis. At pHs 1.8 and 2.2, peak absorbance was at (b) (4) compared with (b) (4) at pH 1.4.
- Method validation parameters included robustness (medium pH, paddle speed), accuracy, repeatability, intermediate precision, linearity and range, specificity, standard and solution stability, and the filtration procedure. All absorbance values were within 97-103% of the target-level absorbance and adequate linearity (correlation coefficient  $\geq 0.99$ ) was observed. (b) (4)

(b) (4) The dissolution data at 30 minutes were less variable.

**Reviewer's Evaluation: Satisfactory.**

- Method (b) (4) SMA.COR.007 was less sensitive to minor buffer pH fluctuations which are expected during routine operations. Given the acceptable sample and standard stability under the Assay conditions, a direct UV analysis approach is acceptable; (b) (4)
- Formal dissolution method discriminating studies as per USP <711> were not completed; however, the Agency is able to infer the method's sensitivity on the basis of the dissolution studies using the (b) (4) Lot8H23/8J16 (b) (4) and Formulation A1, which was composed of a different (b) (4). In these dissolution studies, the pH 1.8 method was able to detect differences.
- The Applicant's justification for selecting a sampling time point of 30 minutes instead of (b) (4) minutes is not acceptable. A dissolution specification should be based on mean data (i.e., Level 2) as per the guidelines outlined in FDA Guidance – Dissolution Testing of Immediate Release Solid Oral Dosage Forms. The mean elution data for the (b) (4) minute sampling time point satisfactorily support a Q (b) (4) and not Q (b) (4). However, the Applicant's proposed specification is acceptable given that the criterion would reject lots not shown to be bioequivalent in Study C-1073-22.



Additionally, the PK data ( $C_{max}$  and  $T_{max}$ ) suggest that tablet dissolution within 30 minutes should be sufficient to ensure that the drug is available for absorption.

- The dissolution stability data support an expiration dating period of 24 months.

### 3.0 REGULATORY ISSUES AND COMMENTS FOR APPLICANT

Deficiencies identified during the review were conveyed to the Applicant, and all issues have been satisfactorily addressed. From CDER-Biopharmaceutics perspective, the NDA is recommended for approval.

The dissolution method recommended for approval is as follows.

(b) (4) SMA.COR.007 Dissolution Method	
<b>Medium</b>	USP pH 1.8 KCl buffer
<b>Apparatus</b>	USP 2 (paddle)
<b>Assay Method</b>	Direct UV, (b) (4) wavelength
<b>Sampling time points</b>	15, 30, 45, 60
<b>Acceptance Criterion</b>	$Q = (b) (4)$ at 30 minutes

Additional advice comments for the applicant are provided below.

- Your proposed dissolution method (b) (4) SMA.COR.007 and acceptance criterion of  $Q = (b) (4)$  at 30 minutes are acceptable. We encourage you to update the analysis method from direct UV to HPLC post approval. (b) (4)



**Dissolution summary data supporting the acceptance criteria for method (b) (4) SMA.COR007 (pH 1.8).**

**Table 4. Dissolution Data (SMA.COR.007) at 15 Minute Sample Point for Primary and Supportive Stability Batches**

Packaged Lot	Time point (months)	Condition	V1	V2	V3	V4	V5	V6	Mean	%RSD	Minimum	Maximum
10C15	17 mo, 11 days	25°C/60%RH	(b) (4)						88	6.4	78	95
10C16	17 mo, 11 days	25°C/60%RH							81	6.8	68	87
10C17	17 mo, 11 days	25°C/60%RH							89	1.0	88	90
10C18	17 mo, 11 days	25°C/60%RH							85	5.6	78	93
10C19	17 mo, 11 days	25°C/60%RH							82	4.9	75	97
10C20	17 mo, 11 days	25°C/60%RH							80	4.6	75	84
8J14	0	25°C/60%RH							92.2	4.0	87.1	97.1
8J14	3	25°C/60%RH							91.6	4.8	85.8	95.4
8J14	6	25°C/60%RH							86.5	5.4	79.6	93.6
8J14	9	25°C/60%RH							96.7	4.0	92.3	102.2
8J14	12	25°C/60%RH							92.4	1.7	90.3	94.5
8J14	18	25°C/60%RH							99	2.3	95	102
8J14	36	25°C/60%RH							94	2.5	90	96
8J15	0	25°C/60%RH							96.0	3.2	93.4	101.9
8J15	3	25°C/60%RH							93.2	4.8	86.3	98.7
8J15	6	25°C/60%RH							87.9	4.5	82.3	92.8
8J15	9	25°C/60%RH							93.4	4.7	89.7	101.0
8J15	12	25°C/60%RH							94.5	1.2	92.9	96.4
8J15	18	25°C/60%RH							100	4.2	95	105
8J15	36	25°C/60%RH							95	2.7	92	98
9J03	Batch release	25°C/60%RH	91.3	3.9	86.5	95.9						
9J03	0	25°C/60%RH	92	4.9	83	96						
9J03	3	25°C/60%RH	98	2.8	94	102						

**Table 4. Dissolution Data (SMA.COR.007) at 15 Minute Sample Point for Primary and Supportive Stability Batches**

Packaged Lot	Time point (months)	Condition	V1	V2	V3	V4	V5	V6	Mean	%RSD	Minimum	Maximum						
9J03	6	25°C/60%RH	(b) (4)						87	5.2	80	93						
9J04	0	25°C/60%RH							93	4.1	85	95						
9J04	3	25°C/60%RH							96	2.9	92	100						
9J04	6	25°C/60%RH							92	3.9	87	96						
10A05	0	25°C/60%RH							87	9.2	72	94						
10A05	3	25°C/60%RH							78	12.0	69	92						
10A06	0	25°C/60%RH							99	1.7	98	102						
10A06	3	25°C/60%RH							86	9.2	73	93						
10A07	0	25°C/60%RH							90	5.2	85	96						
10A07	3	25°C/60%RH							87	6.7	76	93						
All Data									91	7.6	68	105						

**Table 5. Dissolution Data (SMA.COR.007) at 30 Minute Sample Point for Primary Registration Stability Batches**

Packaged Lot	Time point (months)	Condition	V1	V2	V3	V4	V5	V6	Mean	%RSD	Minimum	Maximum
10C15	17 mo, 11 days	25°C/60%RH	(b) (4)						97	2.2	94	98
10C16	17 mo, 11 days	25°C/60%RH							97	2.2	93	96
10C17	17 mo, 11 days	25°C/60%RH							98	0.6	98	99
10C18	17 mo, 11 days	25°C/60%RH							96	1.9	94	96
10C19	17 mo, 11 days	25°C/60%RH							96	2.2	93	98
10C20	17 mo, 11 days	25°C/60%RH							98	0.7	97	98
8J14	0	25°C/60%RH							98.0	2.9	93.5	98.3
8J14	3	25°C/60%RH							91.0	4.0	85.3	92.5
8J14	6	25°C/60%RH							91.8	4.3	86.6	89.9
8J14	9	25°C/60%RH							95.2	5.3	87.9	98.0
8J14	12	25°C/60%RH							96.7	1.4	94.3	98.1
8J14	18	25°C/60%RH							105	3.2	100	102
8J14	36	25°C/60%RH							97	2.1	94	98
8J15	0	25°C/60%RH							98.3	2.6	95.2	99.0
8J15	3	25°C/60%RH							92.7	5.3	85.2	94.6
8J15	6	25°C/60%RH							91.4	3.3	86.7	90.0
8J15	9	25°C/60%RH							93.1	3.8	90.2	90.9
8J15	12	25°C/60%RH							96.4	1.6	93.8	96.0
8J15	18	25°C/60%RH							104	3.5	99	107
8J15	36	25°C/60%RH							97	1.5	94	97
9J03	Release	25°C/60%RH	95.8	2.5	93.0	93.0						
9J03	0	25°C/60%RH	93	3.9	87	92						

**Table 5. Dissolution Data (SMA.COR.007) at 30 Minute Sample Point for Primary Registration Stability Batches**

Packaged Lot	Time point (months)	Condition	V1	V2	V3	V4	V5	V6	Mean	%RSD	Minimum	Maximum						
9J03	3	25°C/60%RH	(b) (4)						102	1.9	99	102						
9J03	6	25°C/60%RH							95	1.5	94	95						
9J04	0	25°C/60%RH							95	2.9	90	97						
9J04	3	25°C/60%RH							101	2.4	97	97						
9J04	6	25°C/60%RH							98	2.8	93	98						
10A05	0	25°C/60%RH							100	2.1	98	100						
10A05	3	25°C/60%RH							98	1.7	96	98						
10A06	0	25°C/60%RH							100	1.6	98	103						
10A06	3	25°C/60%RH							97	2.6	92	98						
10A07	0	25°C/60%RH							99	2.3	97	98						
10A07	3	25°C/60%RH							98	1.8	96	97						
All Data									97	4.2	85	109						

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/s/  
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MINERVA HUGHES  
12/23/2011

ANGELICA DORANTES  
12/23/2011

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number:** 202107

**Applicant:** Corcept Therapeutics **Stamp Date:** 18 April 2011

**Drug Name:** (b) (4)

**NDA Type:** NDA 505(b)2

This 505(b)(2) application for (b) (4) (mifepristone) relies in part on the nonclinical fertility and teratogenicity data in the Mifepex<sup>®</sup> label (NDA 20687; mifepristone; Population Council). The nonclinical toxicology studies conducted under IND 76480 are considered sufficient to bridge the nonclinical findings in the Mifepex<sup>®</sup> label to (b) (4).

Given that Mifepex<sup>®</sup> was approved for an acute indication, the sponsor conducted a 12-month toxicology study in dogs and 2-year carcinogenicity studies in the mouse and rat to support the proposed chronic indication for the treatment of Cushing's syndrome. The sponsor also conducted two *in vitro* hERG studies, a pharmacokinetic study in the dog, several repeat dose toxicology studies in the mouse, rat, dog, and monkey, and two *in vitro* genotoxicity studies (bacterial mutation and chromosome aberration) in support of this application.

The sponsor submitted an independent peer review report (unblinded) by specialists in ocular pathology who reviewed microscope slides of the globe and optic nerve from the albino rats and mice of the 2-year carcinogenicity studies.

The drug substance used in the nonclinical studies was synthesized (b) (4). Proposed commercial formulation is sourced from (b) (4). There are no significant differences in the impurity profiles. Differences between the early formulation and the proposed commercial formulation were evaluated in a single-dose, three-way crossover bioavailability study in healthy volunteers (Study C1073-22).

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		All toxicology study reports were submitted in paper. SAS datasets for carcinogenicity studies submitted electronically.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		Sponsor submitted a 12-month toxicology study in dogs and 2-year carcinogenicity studies in the rat and mouse to support a chronic use indication for mifepristone.

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	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		Oral dosing (intended route of human exposure) was used for pivotal nonclinical studies.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		All pivotal studies ( <i>in vitro</i> hERG study, 12-month dog toxicology study, 2-year rat and mouse carcinogenicity studies, <i>in vitro</i> genotoxicity studies [2]) were conducted in accordance with the GLP regulations.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		Sponsor included full histopathological assessment of the low- and mid-dose groups of the mouse carcinogenicity study (due to premature mortality in the high-dose group) as requested by the Agency.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Proposed draft labeling was submitted.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

# PHARMACOLOGY/TOXICOLOGY 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.

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Reviewing Pharmacologist

Date

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Team Leader/Supervisor

Date

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/s/  
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PATRICIA M BRUNDAGE  
06/21/2011

TODD M BOURCIER  
06/22/2011  
p/t fileable