CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202107Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW
MEMORANDUM
(Addendum to the original review dated to 1/13/2012)

NDA:202107	**Submission Date: April 18, 2011**
Brand Name	**Korlym™**
Generic Name	**Mifepristone**
Reviewer	**Jee Eun Lee, Ph.D.**
Team Leader (Acting)	**Jayabharathi Vaidyanathan, Ph.D.**
OCP Division	**Clinical Pharmacology II**
OND Division	**Metabolism and Endocrinology Products**
Sponsor	**Corcept Therapeutics**
Relevant IND, NDA	**NDA 20687 (Mifeprex); IND 76480 (Korlym)**
Submission Type	**Original NDA 505(b)(2)**
Formulation; Strength(s)	**Tablets for immediate release; 300 mg**
Route of Administration	**Oral**
Indication	**Cushing's syndrome for patients who have not adequately responded to surgery** (b) (4) [redacted]

This is an addendum to the Clinical Pharmacology Review for NDA 202107 dated 1/13/2012 and includes recommendations on the sponsor's proposed labeling.

Summary of Labeling Recommendations

'Strikethrough red' text is for statements recommended to be deleted and 'blue color' text is for statements recommended to be added.

(b) (4)

[redacted]

9 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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/s/

JEE E LEE
01/23/2012

JAYABHARATHI VAIDYANATHAN
01/23/2012

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Division Director	**Chandrahas Sahajwalla, Ph.D.**
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Background:

Refer to Clinical Pharmacology review dated 1/13/12 in DARRTS for Clinical Pharmacology details of mifepristone. The purpose of this addendum is to summarize the Clinical Pharmacology related post marketing study requirement.

1. Phase IV Requirements

Mifepristone is a substrate of CYP 3A4 and its three major active metabolites are formed via CYP3A4-mediated metabolism. Sponsor conducted a drug-drug interaction study with cimetidine, a mild CYP3A inhibitor. There was no effect of cimetidine on mifepristone exposure. The effect of moderate or strong CYP3A inhibitors on the pharmacokinetics of mifepristone has not been evaluated. Sponsor has proposed to [redacted] (b) (4). Since ketoconazole, [redacted] nical management of Cushing's disease, there is a high potential of its concomitant use with mifepristone. The degree of change in exposure of mifepristone when co-administered with strong CYP3A inhibitors is unknown and may present a safety risk or deprive the patients on strong inhibitors the use of Mifepristone due to lack of accurate knowledge of this potential drug

Reference ID: 3074721

interaction. Thus, the quantitative data for effect of ketoconazole on the pharmacokinetics of mifepristone would be beneficial to the target populations. A drug-drug interaction study with ketoconazole is recommended as a Post Marketing Requirement (PMR). The goal of this study is to get a quantitative estimate of the change in exposure of mifepristone following co-administration with ketoconazole. Based on the results of this study, the effect of moderate CYP3A inhibitors on mifepristone pharmacokinetics may need to be addressed. This will help provide more therapeutic options available to Cushing's patients and appropriate labeling of mifepristone when co-administered with CYP3A inhibitors.

Reference ID: 3074721

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/s/

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01/20/2012

JAYABHARATHI VAIDYANATHAN
01/20/2012

CHANDRAHAS G SAHAJWALLA
01/20/2012

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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Table of Contents

1 EXECUTIVE SUMMARY 3

1.1 Recommendation 4

1.2 Phase IV Requirements 4

2 QUESTION BASED REVIEW 6

2.1 General Attributes 6

2.1.1 What the chemistry and physicochemical properties of the drug substance? 6

2.1.2 What is the proposed mechanism of action and therapeutic indication? 7

2.1.3 What are proposed dosage and routes of administration? 8

2.1.4 Is there any DSI inspection requested for any of the clinical studies? 8

2.2 General Clinical Pharmacology 8

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing? ... 9
2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints)? ... 10
2.2.3 What are characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy/safety? ... 11
2.2.4 What are the pharmacokinetic characteristics? ... 15

2.3 Intrinsic factors ... 23

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety response? ... 23
2.3.2 Should dose of mifepristone be adjusted in patients with severe hepatic impairment? ... 24
2.3.3 Should dose of mifepristone be adjusted in patients with renal impairment? ... 25
2.3.4 Is there any effect of gender or race on mifepristone PK? ... 25

2.4 Extrinsic factors ... 25

2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses? ... 26
2.4.2 Should dose of mifepristone be adjusted with concomitant use of strong, moderate, and mild CYP3A4 inhibitors? ... 31
2.4.3 Are DDI studies with moderate and/or strong CYP3A4 inhibitors needed? ... 32
2.4.4 Should CYP2B6 substrates such as bupropion and efavirenz be avoided? ... 32
2.4.5 Should dose of CYP2C8/9 substrates be adjusted or use of CYP3A4 substrates be contraindicated with concomitant use of mifepristone? ... 33

2.5 General Biopharmaceutics ... 33

2.5.1 Based on the biopharmaceutics classification system principles, under which category is this drug classified? ... 33
2.5.2 What are protein-binding properties of the drug? ... 34

2.6 Analytical Section ... 35

2.6.1 What bioanalytical methods are used to assess the drug concentrations? ... 35

REFERENCE: ... 36

3 LABELING ... 36

4 APPENDIX ... 36

4.1 Individual Clinical Study Review ... 36

4.1.1 C-1073-05: Effect of Hepatic Impairment Study with Subjects with Child-Pugh B ... 37
4.1.2 C-1073-19: Effect of Renal Impairment Study ... 42
4.1.3 C-1073-25: DDI with Simvastatin ... 49
4.1.4 C-1073-23: DDI with Digoxin ... 54
4.1.5 C-1073-24: DDI with Alprazolam ... 58
4.1.6 C-1073-26: DDI with Cimetidine ... 65
4.1.7 C-1073-16: DDI with Fluvastatin ... 71
4.1.8 C-1073-20: Food Effect Study with 1200 mg Dose ... 74
4.1.9 C-1073-27: Food Effect with 1200 mg/day Multiple Dose ... 81
4.1.10 C-1073-12: Food Effect Study with 600 mg Dose ... 85
4.1.11 C-1073-22: Bioavailability Comparison for Three Formulations ... 87
4.1.12 C-1073-425: Multiple dose study at 600 mg/day to assess effects on high-density lipoproteins ... 90
4.1.13 Summary of *In Vitro* Studies ... 93

4.2 Cover Sheet and OCP Filing ... 97

Reference ID: 3072217

1 Executive Summary

Corcept Therapeutics submitted the NDA 20-2107 for Korlym with intended indication of the treatment of Cushing's syndrome for patients who have not adequately responded to surgery (b) (4) [redacted].

Mifepristone is approved in US (Mifeprex® tablet (200 mg strength), NDA 20-687) for use in termination of pregnancy (through 49 days' pregnancy) in conjunction with misoprostol. The recommended dose for the termination of pregnancy is a single dose of 600 mg.

(b) (4) [redacted]

Mifepristone is a glucocorticoid receptor (GR-II) antagonist and acts as an antagonist of the progesterone receptor. Mifepristone likely competes with cortisol to its intracellular receptor, the GR-II, preventing the biological activity of cortisol. Cushing's syndrome results from chronic exposure to excessive circulating levels of glucocorticoids. Patients with Cushing's syndrome often show non-specific symptoms such as obesity, muscle weakness, and depression. High level of cortisol may cause diabetes and high blood pressure. The first line of treatment for Cushing's syndrome is surgical removal of the pituitary tumor or the entire pituitary.

The sponsor proposes the use of mifepristone for medical treatment for patients with Cushing's disease who have not adequately responded to or relapsed after surgery, (b) (4) [redacted] The sponsor received orphan designation for these indications.

To support the efficacy in Cushing's syndrome, the sponsor conducted one 24-week, open-label, uncontrolled Phase 3 clinical trial in 50 patients with Cushing's syndrome: 29 patients with diabetes and 21 patients with hypertension. The Phase 3 clinical trial shows beneficial effects of mifepristone in mitigating hypercortisolemia.

The recommended dose titration scheme is the same as that used in the Phase 3 trial: 300 mg to 1200 mg based on tolerability and dose cap of 900 mg for patients with body weight < 60 kg.

The pharmacokinetics of mifepristone has been evaluated in thirteen studies with healthy subjects, subjects with severe renal impairment, moderate hepatic impairment. Mifepristone shows nonlinear pharmacokinetics and time-dependent pharmacokinetics. The major route of elimination is metabolism and three active metabolites produced by CYP3A4-mediated metabolism have been identified. *In vitro* studies submitted by the

Reference ID: 3072217

sponsor indicate mifepristone is an inhibitor of CYP3A4 and CYP2C8, its metabolites are inhibitors of CYP3A4, CYP2C8/9, CYP2C19, and CYP 2A6. Furthermore, mifepristone is substrates for P-glycoprotein and breast cancer resistance protein (BCRP).

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-II (OCP/DCP-II) has reviewed the clinical pharmacology data submitted under NDA 202107 dated 4/18/2011 and finds it acceptable.

1.2 Phase IV Requirements

Mifepristone is a substrate of CYP 3A4 and its three major active metabolites are products of CYP3A4-mediated metabolism. Mifepristone is also an inhibitor of CYP3A4. The effect of a strong CYP3A4 inhibitor such as ketoconazole on the pharmacokinetics of mifepristone has not been evaluated. Sponsor proposes (b) (4) Since ketoconazole is being used in the management of Cushing's disease, there is a potential of its concomitant use with mifepristone. The need of conducting a drug-drug interaction study with ketoconazole as a PMR is being discussed internally and will be finalized following the wrap-up discussion with the review team and the decision will be reflected as an addendum to Clinical Pharmacology review.

1.3 Clinical Pharmacology Summary

The current submission consisted of 18 clinical pharmacology studies including a thorough QTc study and five *in vitro* studies. Mifepristone was approved as a single dose regimen for termination of pregnancy and its multiple-dose pharmacokinetics and drug-drug interactions with drugs that are frequently prescribed to the target population, patients with Cushing syndrome, are major parts of the clinical pharmacology programs in the current submission.

The PK parameters of mifepristone following single dose of 600 mg are summarized in Table 1 and the PK profiles of mifepristone following single dose of 600 mg is shown in Figure 1 along with that of last dose of multiple doses of 600 mg of mifepristone for 7 days in healthy volunteers. The detailed PK parameters and profiles of metabolites of mifepristone are summarized in 2.2.4.

Table 1. Summary of Pharmacokinetic Parameters of Mifepristone Following Single Dose of 600 mg in Healthy Subjects (Mean (SD), Source: Reviewer's Analysis)

Pharmacokinetic parameters	Dosing Regimen	
	Single Dose	Multiple Dose

Reference ID: 3072217

$AUC_{0-\infty}$ (hr*ng/mL)	170059 (61717)	369177 (205164)
AUC_{0-last} (hr*ng/mL)	164816 (60913)	323797 (146061)
Cmax (ng/mL)	2982.3 (1040)	3329.3 (1259)
Tmax (hr)*	1.25 [0.5, 6]	1 [0.5, 2]
$t_{1/2}$ (hr)	40.7 (14.6)	84.6 (60.9)

*Median with range

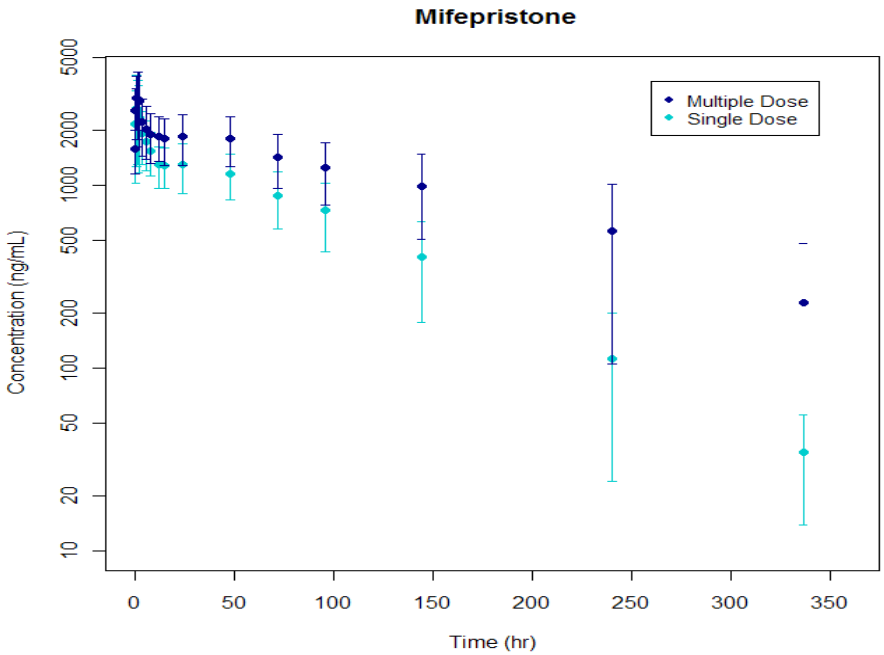


Figure 1. Pharmacokinetics profiles of mifepristone following single dose of mifepristone 600 mg or multiple doses of mifepristone 600 mg/day for 7 days (source: C-1073-05)

Simvastatin: The exposure of simvastatin and simvastatin acid (AUC) was increased greater than 10-fold and 15-fold, respectively following 80 mg of simvastatin co-administered with multiple doses of mifepristone (1200 mg/day) compared to that following 40 mg of simvastatin only.

Fluvastatin: Following the first and last dose of mifepristone 1200 mg/day given for 7 days, there was a 2.67-fold and 3.57 fold increase, respectively, in AUC_{0-24} of fluvastatin.

Digoxin: The drug-drug interaction study with digoxin did not find significant effect of mifepristone on digoxin pharmacokinetics.

Alprazolam: The exposure of alprazolam is expected to increase approximately 2-fold with concomitant administration of mifepristone.

Cimetidine: No evidence for the effect of cimetidine, a mild inhibitor of CYP3A4, on the pharmacokinetics of mifepristone was observed.

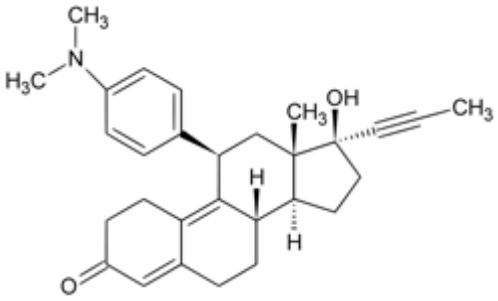
Reference ID: 3072217

Hepatic/renal impairment: No dose adjustment of mifepristone is recommended to subjects with renal impairment, but the sponsor set the maximum dose as 600 mg per day. No dose adjustment of mifepristone is recommended to patients with mild/moderate hepatic impairment, but the maximum dose should be set to 600 mg per day as it is to patients with renal impairment. The administration of mifepristone to patients with severe hepatic impairment is not recommended

2 Question Based Review

2.1 General Attributes

2.1.1 What the chemistry and physicochemical properties of the drug substance?



Chemical Structure:

11β-[p-(Dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one (IUPAC)

Mifepristone is derived from the naturally occurring material, estrone, and is structurally similar to progesterone and glucocorticoids. Mifepristone is an antagonist of the progesterone receptor at low doses and an antagonist of the glucocorticoid receptors at higher doses. Mifepristone has five chiral centers with the absolute stereochemistry 8S, 11R, 13S, 14S, 17S. The sponsor claimed the absolute stereochemistry is believed to be preserved *in vivo*, which is preserved in the six metabolites. The CMC review team also confirmed that *in vivo* chiral conversion of mifepristone that generates altered pharmacological activity of the drug is not anticipated.

Mifepristone is a weak base with a pKa of approximately 5.0 and demonstrates a pH-dependent solubility profile. At pH=1.5, the solubility is ~25 mg/mL and declined as pH increases. At pH=2.5 and above, the solubility is less than 1 mg/mL. The logarithm of the partition coefficient between n-octanol and water of mifepristone is 5.13.

Reference ID: 3072217

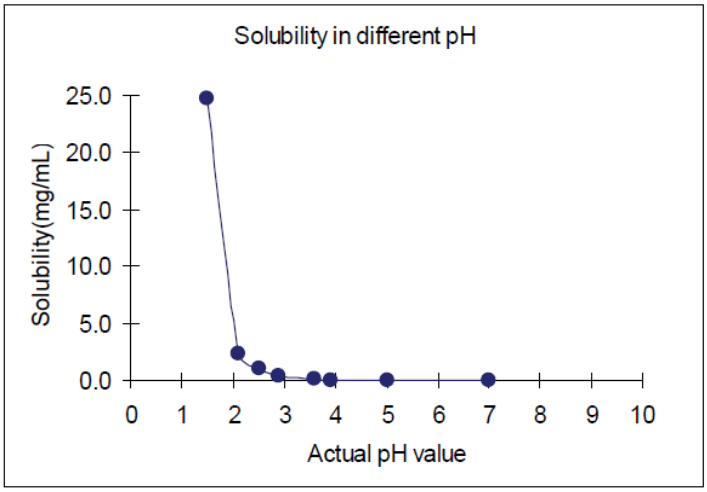


Figure 2. pH- dependent solubility profile of mifepristone at ~25°C

2.1.2 What is the proposed mechanism of action and therapeutic indication?

The proposed indication of the current NDA of oral administration of mifepristone is to treat clinical and metabolic effects of hypercortisolism with endogenous Cushing's syndrome.

Glucocorticoid cortisol, secreted from the zona fasciculate and reticularis of the adrenal gland under the stimulus of adrenocorticotropic hormone (ACTH) from the pituitary gland is the end product of the hypothalamo-pituitary-adrenal (HPA) axis. ACTH is then secreted in response to corticotropin releasing hormone (CRH) and vasopressin from the hypothalamus. Cortisol exerts negative feedback control on both CRH and vasopressin in the hypothalamus, and ACTH in the pituitary. In normal individuals, cortisol is secreted in a circadian rhythm; levels fall during the day from a peak in the morning to a ground at midnight; they then begin to rise again in the afternoon. If this circadian rhythm is lost along with the feedback mechanism, excessive levels of cortisol may render "endogenous" Cushing's syndrome. Administration of excessive quantity of glucocorticoid may lead to similar symptoms, which is called "exogenous" Cushing's syndrome.

Pituitary-dependent Cushing's syndrome, known as Cushing's disease, is the most common, which accounts for 60-80% of the cases. It is usually due to a monoclonal corticotroph adenoma. ACTH-independent causes of Cushing's syndrome apart from exogenous glucocorticoids are various. The most common cause is an adrenal adenoma or carcinoma.

The treatment of choice for Cushing's disease is trans-sphenoidal surgery. The overall remission rate is about 70%, and ~25% of them have a recurrence within 10 years of post-surgery. The mortality rate associated with the surgery is about 2% and other major complications occur at 15% rate. The treatment of choice for all cases of ACTH-independent Cushing's syndrome is adrenalectomy. Patients with adrenal adenomas show

Reference ID: 3072217

100% recovery rate following the surgery, with low morbidity and mortality. Conventional radiotherapy is also accompanied.

In patients who failed in responding surgery and/or radiotherapy, medical management is recommended prior to bilateral adrenalectomy. Inhibitors of steroid biosynthesis in the adrenal cortex are used, and the most commonly used agents are metyrapone, ketoconazole, and mitotane (BA Gross et al., 2007). Ketoconazole is believed to have a direct effect on ACTH secretion from a thymic carcinoid tumor.

Mifepristone is a cortisol receptor blocker and it is suggested to treat the clinical and metabolic effect of hypercortisolism in patients with endogenous Cushing's syndrome, including:

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

(b) (4)

Mifepristone has a high affinity for the receptors of glucocorticoids (cortisol) and progesterone, and competes with these endogenous steroids for binding sites (Philibert et al,, 1985). The glucocorticoid-blocking effects of mifepristone occur at doses that those required to block progesterone. Mifepristone does not decrease cortisol production. Glucocorticoids modulate gene expression by interacting with a glucocorticoid receptor, followed by "transformation" of the steroid-receptor complex into a form capable of nuclear binding. Mifepristone appears to exert its antiglucocorticoid effects both by preventing complete glucocorticoid receptor transformation and by altering a step subsequent to binding of the glucocorticoid receptor with DNA.

2.1.3 What are proposed dosage and routes of administration?

Mifepristone is orally administered with recommended initial dose of 300 mg once daily. Further escalation in 300-mg increments to a maximum of 1200 mg once daily may be appropriate in some patients, with increased monitoring for risk factors associated with the drug. Korlym should be given as a single daily dose and recommended to be given with a meal for more consistent exposure.

2.1.4 Is there any DSI inspection requested for any of the clinical studies?

No. The Phase 3 study used the final to-be-marketed formulation.

2.2 General Clinical Pharmacology

Reference ID: 3072217

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing?

One Phase 3 clinical efficacy trial (C-1073-400) in patients with Cushing's syndrome has been completed and a long-term extension study (C-1073-415) is ongoing. Study C-1073-400 was a 24-week, open-label study where 50 subjects were assigned to receive an initial dose of 300 mg mifepristone once daily (QD) following screening period. In search of the optimal dose, dose escalation was undertaken under clinical monitoring. After 14 days of dosing at 300 mg QD, dose escalations in 300-mg increments were made every four weeks if no clinical improvement was seen and if the drug was well tolerated. Dose escalation was not required to patients who showed significant clinical improvement at the current dosing level. The primary endpoints were glucose homeostasis in diabetes cohort and blood pressure in hypertensive cohort. The secondary endpoints for clinical improvements included body weight, body composition, body strength, and psychiatric symptoms etc. The maximum dose to be used was 1200 mg QD (or 900 mg QD for subjects weighing < 60 kg). In cases of severe hypercortisolism, the dose of mifepristone could have been increased further with the approval of the medical monitor; however, the dose was not to be increased beyond a weight-adjusted dose of 20 mg/kg per day. Subjects who completed the study were to enter the extension study (C-1073-415) for evaluation of long-term safety of mifepristone of the signs and symptoms of endogenous Cushing's syndrome and persistence of therapeutic benefit of mifepristone treatment. The initial dose of mifepristone for the extension study was the same dose that was being administered at the Week 24 visit in study C1073-400.

Thirteen clinical pharmacology studies have been submitted under the current NDA.

- C-1073-05 PK (single and multiple dose) in hepatically impaired and healthy subjects
- C-1073-12 Food effect for a 600 mg single dose
- C-1073-16 Drug interaction study: fluvastatin (CYP2C9 substrate)
- C-1073-19 PK (multiple dose) in renally impaired and healthy subjects
- C-1073-20 Food effect for a 1200 mg single dose: Dose effect for single doses of 300, 600, or 1200 mg
- C-1073-22 Bioavailability study of effect of formulation change
- C-1073-23 Drug interaction study: digoxin (P-gp substrate)
- C-1073-24 Drug interaction study: alprazolam (CYP3A substrate)
- C-1073-25 Drug interaction study: simvastatin (CYP3A substrate)
- C-1073-26 Drug interaction study: cimetidine (CYP3A inhibitor)
- C-1073-27 Food effect for multiple doses of 1200 mg/day
- C-1073-300 Thorough QT study in healthy volunteers - multiple doses of 600 or 1800 mg/day
- C-1073-425 Multiple dose study at 600 mg/day to assess effects on high-density lipoproteins

Dose recommendations in the proposed labeling are in agreement with Phase 3 clinical trial for general population and results obtained from clinical pharmacology studies are

Reference ID: 3072217

reflected in sections for contraindications, drug-drug interactions, and specific populations.

The dose recommendations proposed by the sponsor are:

(b) (4)

[redacted]

During the pre-NDA meeting on September 4, 2010, recommendations from clinical pharmacology were made to the sponsor, which included:

- DDI studies as guidance recommends including with a strong inhibitor of CYP3A4
- PK sampling in Phase 3 trial was recommended for covariate analysis
- Evaluation of hepatic impairment at all stages

The sponsor did not conduct any additional DDI studies after the meeting. Instead, they briefly addressed the interaction potential using concentrations of mifepristone in one patient who was on ketoconazole (400 mg TID). Samples were collected for PK evaluation in Phase 3 trial but no population pharmacokinetic analysis was performed. Non-parametric covariate analysis was performed with pre-dose concentrations only.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints)?

The primary endpoints in the Phase 3 protocol are (1) change in $AUC_{glucose}$ during the oral glucose tolerance test (OGTT) in diabetes (DM) cohort (2) change in diastolic blood pressure in hypertensive (HT) cohort. The success of the study was evaluated by the responder analysis: subjects were defined as responders if they had (1) greater than 25%

Reference ID: 3072217

decrease in $AUC_{glucose}$ in DM cohort (2) greater than 5 mmHg decline in diastolic blood pressure in HT cohort. A key secondary endpoint was an assessment of clinical improvement determined at every visit by the Data Review Board.

2.2.3 What are characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy/safety?

In study C-1073-400, mifepristone doses of 300, 600, 900, and 1200 mg were administered based on tolerability and clinical response. To determine how mifepristone exposure changes as dose changes, reviewer's analysis was performed using the data of patients in DM cohort. As seen in Figure 3, there is no strong indication for increase in exposure in both responders and non-responders whose dose was increased from 300 mg to 1200 mg over time (top left panel in Figure 3). The distribution of responders is close to the central tendency (lowess line) and the exposure of non-responders was higher than average in patients whose maximum escalated dose was 300 mg (lower right panel in Figure 3).

Reference ID: 3072217

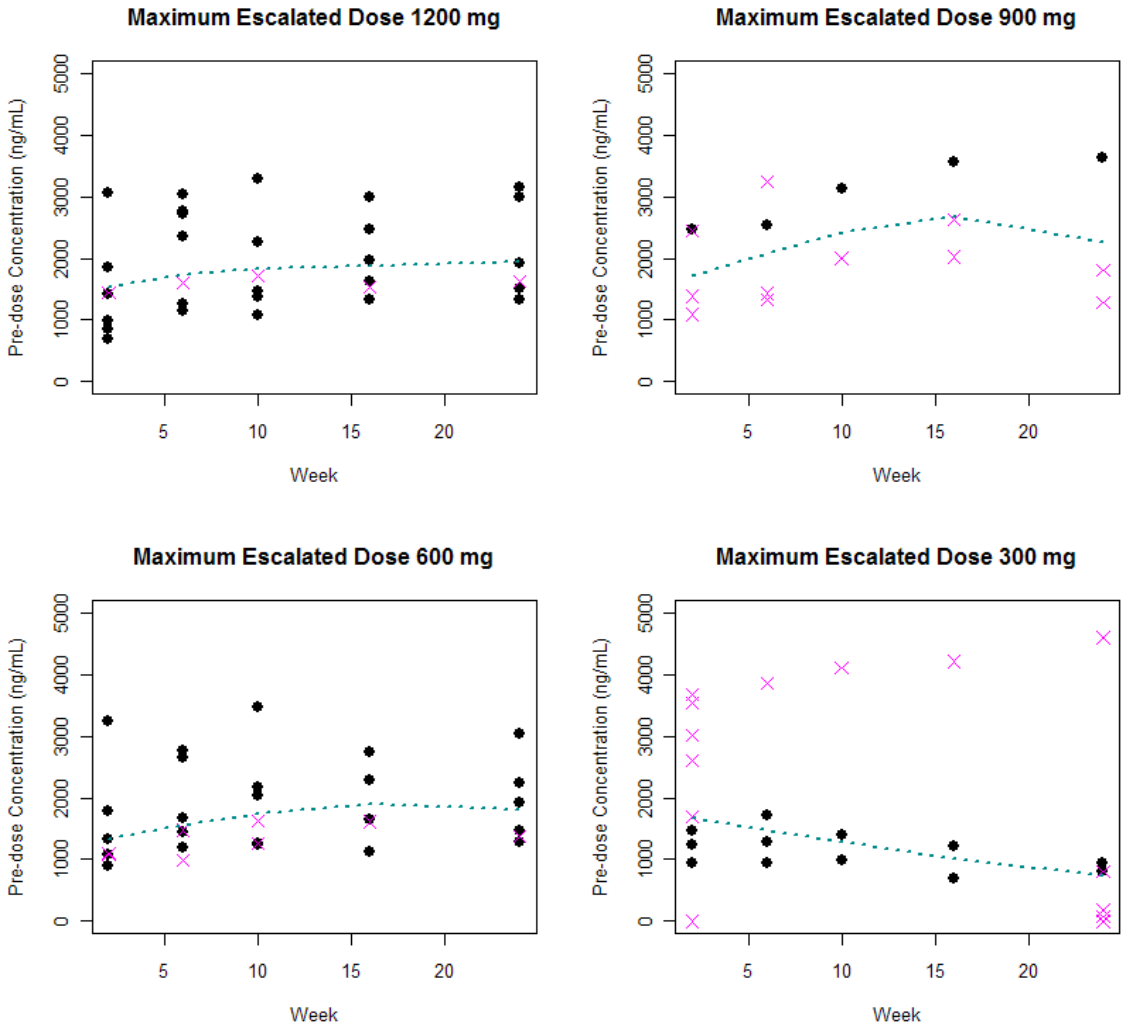
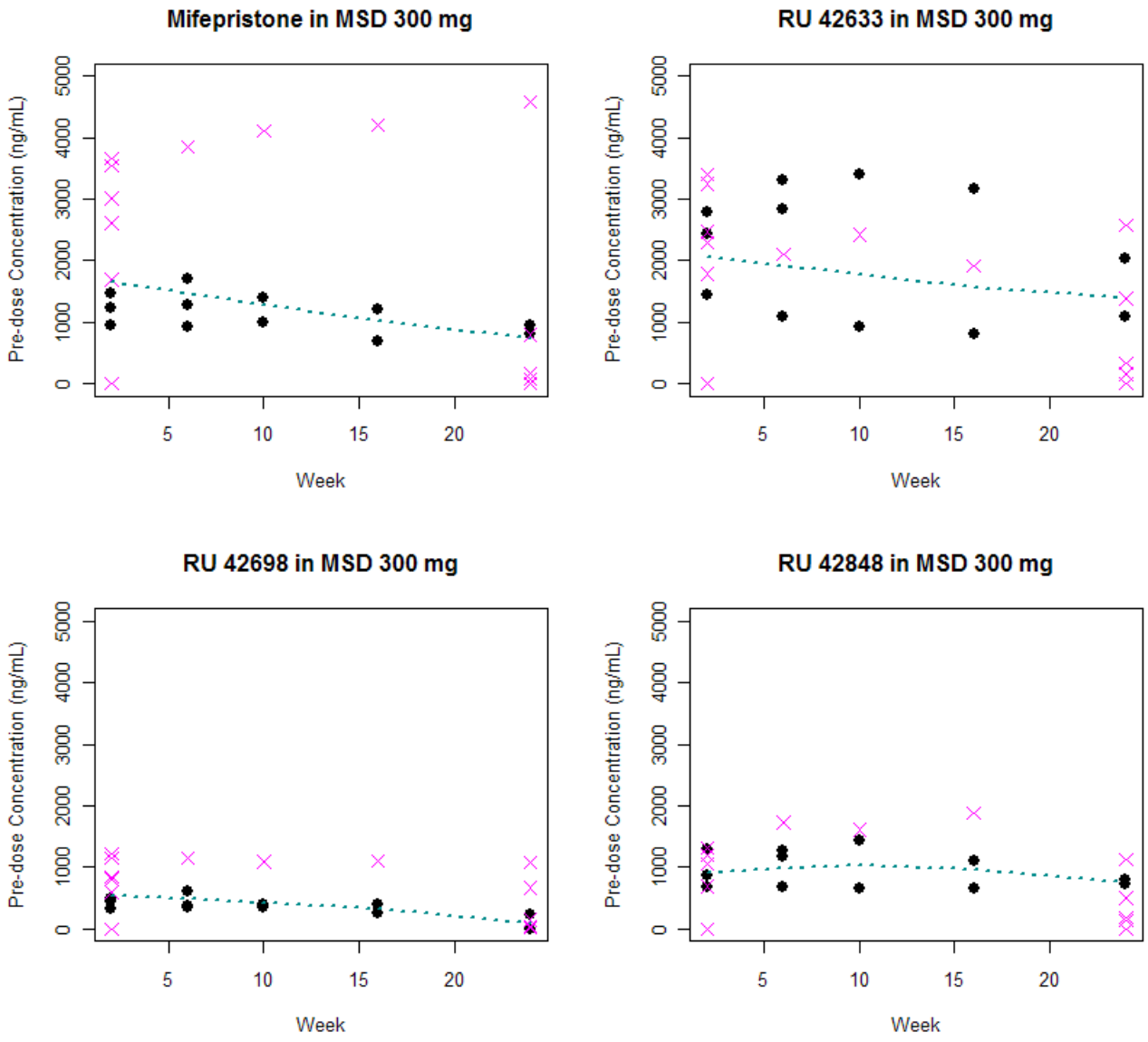
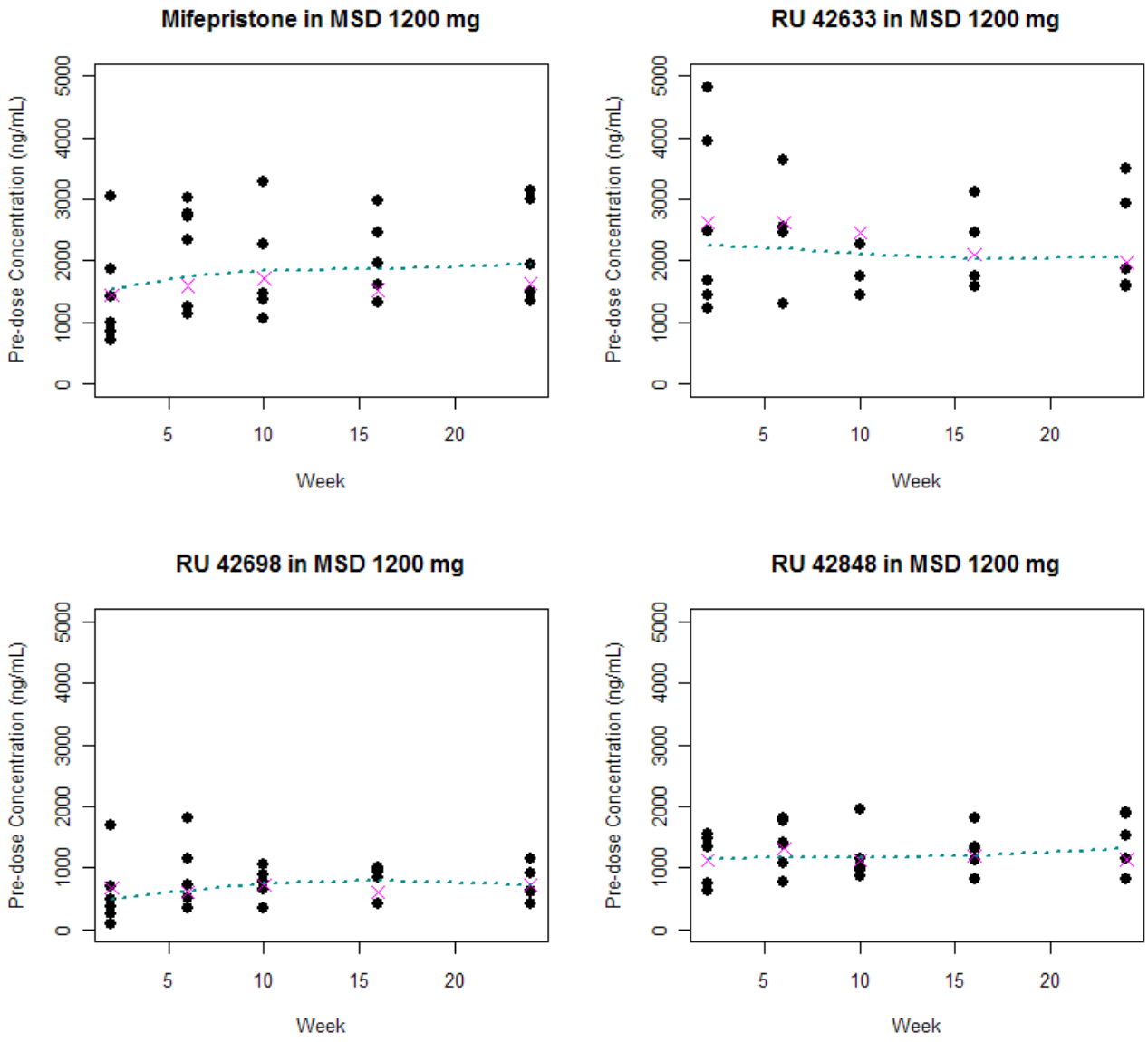


Figure 3. Trough concentrations of mifepristone over time in patients whose maximum dose was 300, 600, 900, and 1200 mg in Study C-1074-400 (two patients who received 150 mg as protocol deviation were excluded)

Since mifepristone metabolites are also active, similar analysis were performed, to see if there is any exposure-response with respect to each metabolite. Figure 4 below shows that similar to the parent, there is a lack of any exposure-response relationship for the three metabolites.


Mifepristone in MSD 300 mg
RU 42633 in MSD 300 mg
RU 42698 in MSD 300 mg
RU 42848 in MSD 300 mg
Pre-dose Concentration (ng/mL)
0
1000
2000
3000
4000
5000
5
10
15
20
Week

(a)



(b)

Figure 4. . Trough concentrations of mifepristone and its metabolites over time in patients whose maximum dose was 300 mg (a) or 1200 mg (b) in Study C-1074-400

To evaluate if body weight is a covariate for the PK exposure of mifepristone, trough concentrations were plotted against body weight of individual patients. As seen in figure 5, body weight does not contribute to the PK exposure of mifepristone.

Reference ID: 3072217

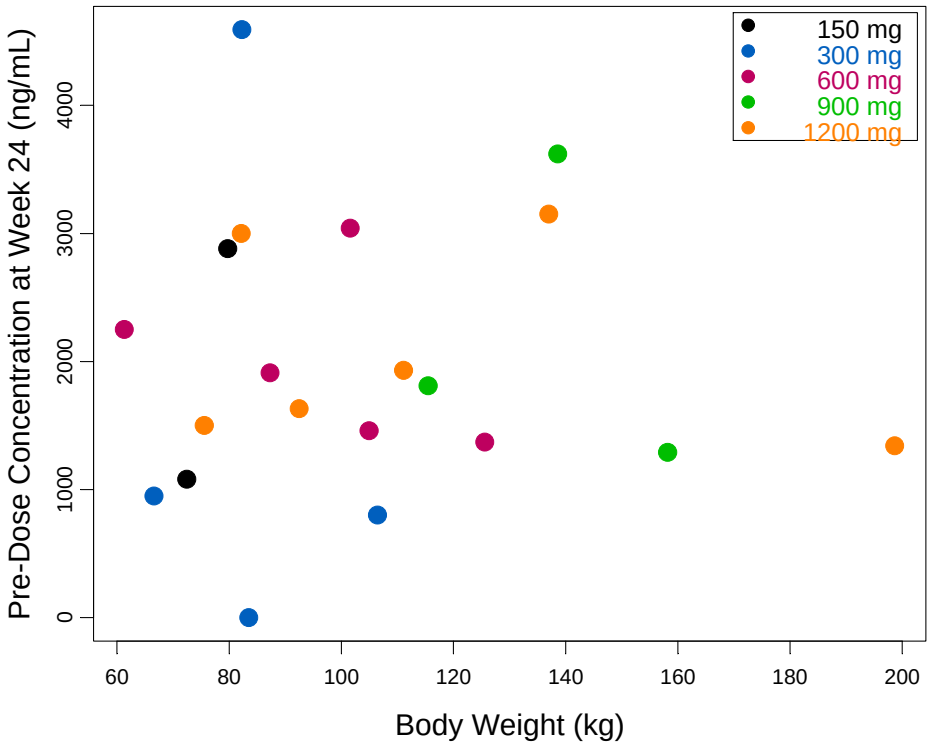


Figure 5. Trough concentrations of mifepristone at Week 24 in patients whose maximum dose was 300, 600, 900, and 1200 mg in Study C-1074-400 (two patients received 150 mg as protocol deviation)

Although the sponsor specified 60 kg body weight for dosing cap of 900 mg, there is no justification for the body weight cut-off. The recommendation was based on dosing cap for 20 mg/kg. No subjects included in Phase 3 study had body weight below 60 kg and the clinical experience above 20 mg/kg is rare according to literature study summary. Thus, this recommendation for dosing seems reasonable.

2.2.4 What are the pharmacokinetic characteristics?

2.2.4.1 What are single- and multiple-dose PK parameters of mifepristone and its metabolites in healthy adults?

Mifepristone is mainly metabolized by CYP3A4 and its metabolites are believed to be pharmacologically active. Mifepristone is rapidly absorbed (Tmax 1~2 hours postdose), and mean Cmax and $AUC_{0\text{-inf}}$ following 600 mg of mifepristone were 2982.3 ng/mL, and 170,059 ng*hr/mL, respectively. Its active metabolites are produced to substantial extent. The peak of RU 42633, RU 42698, and RU 42848 were observed around 4, 6, and 36 hours, respectively. The $AUC_{0\text{-inf}}$ of RU 42633 was greater than the parent compound while Cmax was slightly lower: 240,533 ng*hr/mL and 2331 ng/mL, respectively. Other two metabolites' PK parameters are summarized in Table 2.

Reference ID: 3072217

Table 2. Summary the plasma PK parameters of mifepristone and its metabolites following single dose of 600 mg of mifepristone

Analyte	Dosing Regimen	$T_{1/2}$ (hr)	Cmax (ng/mL)	Tmax (hr)[a]	$AUC_{0\text{-last}}$ (ng*hr/mL)	$AUC_{0\text{-inf}}$ (ng*hr/mL)
Mifepristone	Single	40.7 (14.6)	2982.3 (1040)	1.25 [0.5, 6]	164816 (60913)	170059 (61717)
RU42633	Single	45.8 (17.7)	2331.0 (456.2)	4 [1.5, 48]	235378 (78996)	240533 (82669)
RU42698	Single	49.5(14.3)	804.1 (291.0)	6 [1.5, 48]	75701 (37773)	79680 (37503)
RU42848	Single	53.3(22.2)	1077.0 (77)	36 [8, 96]	159092 (60058)	167091 (68866)

[a] Median with range

2.2.4.2 Based on PK parameters reported, has dose proportionality in healthy adults and patients established?

The sponsor discussed dose-proportionality using summarized PK of mifepristone by analysis of pooled data obtained from various studies in fasted healthy volunteers or patients receiving single or multiple doses of mifepristone. Statistical comparisons of Cmax, $AUC_{0\text{-}24hr}$ and Ctrough (pre-dose at Day 7) at the dose levels of 300, 600, 1200, and 1800 mg was conducted and concluded that dose-adjusted PK parameters showed statistically significant difference across the three dose levels. The sponsor concluded the mifepristone exposure showed increment in less than dose-proportional manner in both healthy adults and patients. Nonetheless, large variability in pharmacokinetic parameters across the studies was observed as shown in the Table 3.

Table 3. Mifepristone Cmax and AUC following Single Doses of 300, 600, and 1200 mg in Healthy Adults in the Fasted State (Source: Table 44 Clinical Pharmacology Summary)

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

Reference ID: 3072217

There is one study where three different doses were administered in healthy subjects: C-1073-020 (Food effect study). In this study, subjects were randomly assigned to receive 300 mg (n=11), 600 mg (n=9) or 1200 mg (n=20) under fasting condition. The dose-normalized Cmax and AUC comparisons indicate that both Cmax and AUC increased less than dose-proportional as dose increased.

The sponsor also used literature data to discuss over the dose-proportionality, which was obtained from a crossover study comparing single doses ranging from 25 to 600 mg in non-pregnant women (Shi YE et al, 1993). There was a 3-fold increase in the Cmax and a 10-fold increase in AUC for mifepristone. From another study where parallel groups of volunteers received 12.5, 25, 50, or 100 mg of mifepristone twice a day for 4 days, 2.3-fold increase in Ctrough over the dose range (Heikinheimo O et al., 1989).

As discussed in 2.2.4.5 (ADME characteristics), the low solubility of mifepristone seems to limit the drug absorption at higher doses. The dose-dependent nonlinearity of mifepristone PK following oral administration of a single dose of 300 mg ~ 1800 mg is specified by less than proportional increase in exposure with increasing dose. If protein binding is saturated at higher doses resulting in rapid drug elimination from plasma, then the exposure might increase less than proportional as dose increase. However, this is not the case since mifepristone clearance is not increased as dose increases. There is no evidence for facilitated transporter(s) responsible for absorption for mifepristone, which may account for the nonlinear PK. Therefore, the low solubility of mifepristone seems to be responsible for dose-dependent PK of mifepristone.

2.2.4.3 What are characteristics of multiple dose pharmacokinetics? Is there accumulation and/or time-dependence?

Not only dose-dependent pharmacokinetics but also time-dependent pharmacokinetics of mifepristone has been observed. Since the sponsor does not seem to have been fully aware that mifepristone is a mechanism-based inhibitor for CYP3A4 and CYP2B6. Since major pathway of mifepristone metabolism is via CYP3A4, the time-dependent PK seems to be mainly accounted for by auto-inhibition on CYP3A4. A detailed summary of PK parameters of mifepristone and its metabolites obtained from multiple-dose studies are summarized from Table 4.

Table 4. Summary the plasma PK parameters of mifepristone and its metabolites following single dose of 600 mg or multiple doses of 600 mg/day of mifepristone for 7 days (source: C-1073-05)

Analyte	Dosing Regimen	$T_{1/2}$ (hr)	Cmax (ng/mL)	Tmax (hr)[a]	$AUC_{0\text{-last}}$ (ng*hr/mL)	$AUC_{0\text{-inf}}$ (ng*hr/mL)
Mifepristone	Multiple	84.6 (60.9)	3329.3 (1259)	1 [0.5, 2]	323797 (146061)	369177 (205164)
	Single	40.7 (14.6)	2982.3 (1040)	1.25 [0.5, 6]	164816 (60913)	170059 (61717)
RU42633	Multiple	113.1 (87.1)	2165.8 (479.5)	5 [2, 48]	373600 (159271)	473514 (291739)
	Single	45.8 (17.7)	2331.0 (456.2)	4 [1.5, 48]	235378 (78996)	240533 (82669)

Reference ID: 3072217

RU42698	Multiple	104.3(75.6)	832.4 (362.3)	6 [2, 24]	139791 (77347)	173097 (119240)
	Single	49.5(14.3)	804.1 (291.0)	6 [1.5, 48]	75701 (37773)	79680 (37503)
RU42848	Multiple	123.4(97.7)	1244.0 (367.6)	15 [4, 48]	237523 (96955)	308736 (183913)
	Single	53.3(22.2)	1077.0 (77)	36 [8, 96]	159092 (60058)	167091 (68866)

[a] Median with range

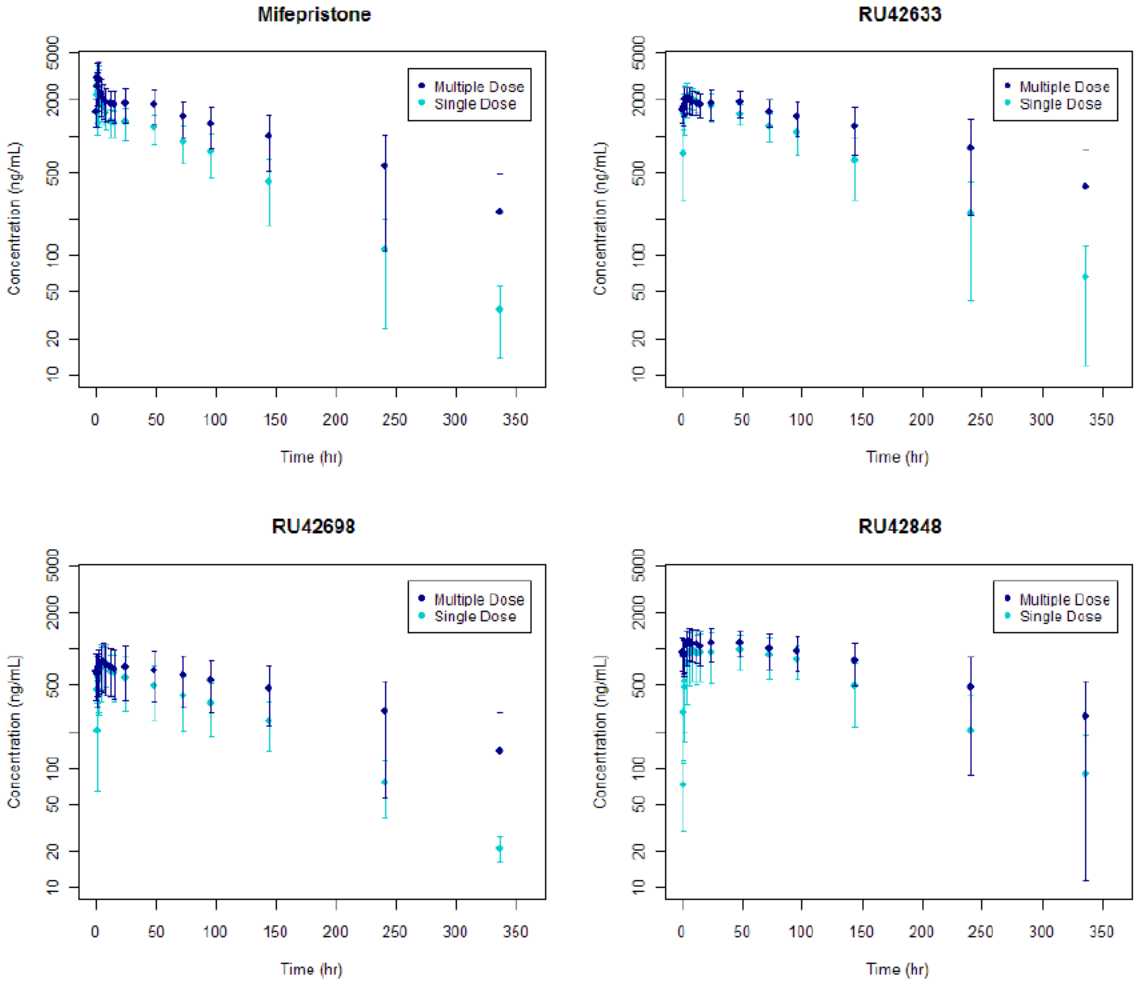


Figure 6. Pharmacokinetics profiles of mifepristone and its metabolites following single dose of mifepristone 600 mg or multiple doses of mifepristone 600 mg/day for 7 days (source: C-1073-05)

The sponsor observed time-dependent PK of mifepristone and its metabolites, but failed to connect those observations to mechanism-based inhibition of CYP3A4 by mifepristone. Mifepristone is believed to irreversibly modify the CYP3A4 apoprotein via producing a reactive ketene intermediate that reacts with a nucleophilic residue at the enzyme (He et al., 1999). It has been reported that inactivation of CYP3A4 by

Reference ID: 3072217

mifepristone is also associated with the formation of a nitrosoalkane-metabolic intermediate complex through the oxidation of the dimethyl-amino moiety, which is major pathway of CYP3A4 inactivation by analogues of mifepristone such as lilopristone and onapristone (Jang and Benet 1998). The reviewer evaluated time-dependent PK using several Phase 1 studies with crossover design with both single dose and multiple dose regimens. Table 4 shows comparison of PK parameters of mifepristone and its metabolite following 7-day daily doses of 600 mg mifepristone compared to single dose of 600 mg mifepristone in healthy subjects.

Table 5. PK parameter comparisons between single-dose and multiple-dose PK (Source: C-1073-005)

Population	Analyte	Parameter	GMLS ratio (Multiple Dose/Single Dose)	90% CI (Multiple Dose/Single Dose)
Healthy Volunteers (n=10)	Mifepristone	Cmax	1.09	0.89-1.33
		AUCinf	2.03	1.61-2.56
		Half-life	1.79	1.29-2.48
	RU 42633	Cmax	0.93	0.81-1.06
		AUCinf	1.76	1.38-2.25
		Half-life	2.03	1.44-2.88
	RU 42698	Cmax	1.00	0.87-1.15
		AUCinf	1.97	1.57-2.48
		Half-life	1.76	1.23-2.53
	RU 42848	Cmax	1.18	1.02-1.37
		AUCinf	1.72	1.30-2.28
		Half-life	1.91	1.40-2.62

Following multiple-dose administration of mifepristone, significant increases in AUCs of all analytes due to the prolonged half-lives have been observed in both healthy volunteers and subjects with moderate hepatic impairment (data for hepatic impairment is not shown in this section) as compared to those following single dose.

To evaluate the half-life change in each individual, spaghetti plots were generated for healthy volunteers in Study C-1073-005. As seen in Figure 7, half-life increase occurred in most individual despite large variability. The similar trend was also observed for subjects with hepatic impairment as well (data and plot not shown). The results indicate that the mechanism-based inhibition of mifepristone on its own metabolism might be responsible for the half-life increase and would be influential for other CYP3A4 substrates.

Reference ID: 3072217

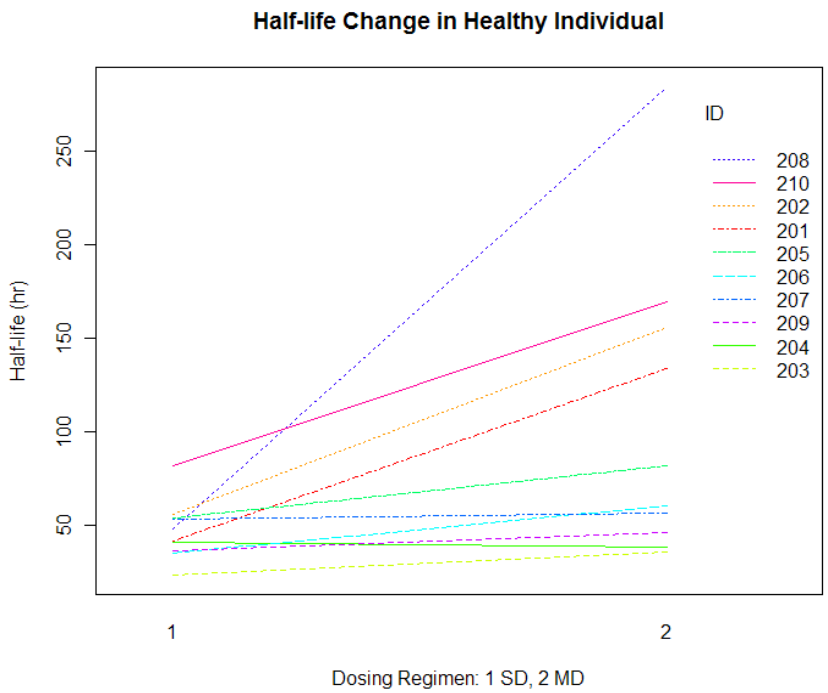


Figure 7. Spaghetti plot for half-life following multiples doses (MD) of 600 mg mifepristone in healthy subjects compared to singles dose (SD) of 600 mg mifepristone. (Reviewer's analysis with data from C-1073-05 study)

2.2.4.4 Have concentrations of mifepristone reached steady state during Phase 3 clinical trial? Are there differences in pharmacokinetics between healthy volunteers and patients?

Theoretically time to reach steady state is approximately 8 days based on $T_{½}$ of 40 hours (half-life following single dose) and 18 days based on $T_{½}$ of 85 hours (half-life following multiple doses of mifepristone 600 mg for 7 days. In the Phase 3 trial, the pre-dose concentrations did not increase significantly as dose was increased above 600 mg and the profiles in patients whose maximum titrated dose was 300 mg indicate that mifepristone concentration tends to decrease over time. These observations are inconclusive as the doses were titrated at various time points and the data are too sparse. Trough concentrations from the Phase 3 study were compared to the pre-dose concentrations observed from two Phase 1 studies including healthy subjects in Study C-1073-05 and Study C-1073-19. On comparison of the pre-dose concentrations on Week 24, there is no significant difference in pharmacokinetics in healthy volunteers and patients (Figure 8). The mean pre-dose concentrations in healthy volunteers on Day 7 following 600 mg and 1200 mg were 1594 ng/mL and 1553 ng/mL, respectively, and in patients with Cushing's syndrome on Week 24 following titration to 600 mg and 1200 mg were 1855 ng/mL and 2001 ng/mL, respectively. Simple two-sample t-test indicates there are no differences in healthy and patients for both dose levels.

Reference ID: 3072217

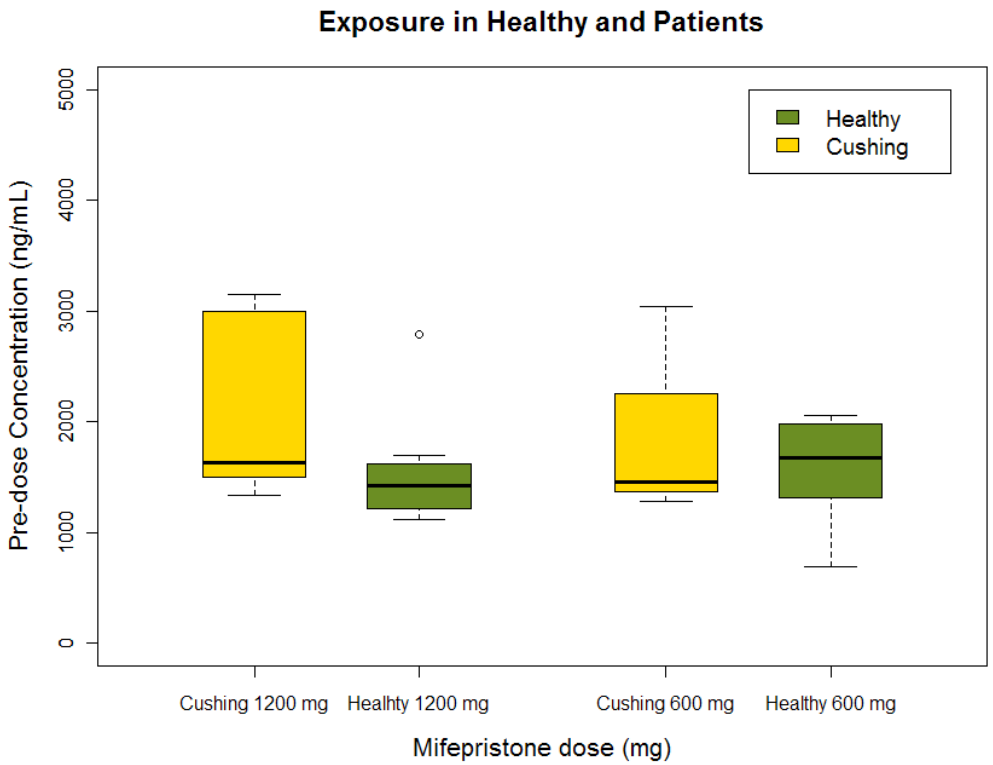


Figure 8. Boxplots for trough concentrations of mifepristone from C-1073-05, C-1073-19, and C-1073-400 studies. (Doses in the studies were 600 mg, 1200 mg in healthy volunteers, and 600 mg to 1200 mg as the maximum escalated doses in patients)

2.2.4.5 What are general ADME characteristics of mifepristone?

- **Absorption**

According to the approved Mifeprex labeling, following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 mg/L occurring approximately 90 minutes after ingestion. Mifeprex summary basis of approval indicates that the absolute bioavailability of 100 mg of mifepristone is approximately 40% (range, 30-56%), while that of lower doses is higher, 72% for 40 mg and 69% for 20 mg. The low solubility of mifepristone is likely to be the limiting factor on absorption with higher doses. This solubility-limited absorption seems to be consistent with the pharmacokinetic data included in the current submission. The dose-dependent nonlinearity of mifepristone PK following oral administration of a single dose of 300 mg ~ 1800 mg is specified by less than proportional increase in exposure with increasing dose. Since drug clearance is not decreased as dose increases, saturation of protein-binding is not likely to contribute to the nonlinear PK. Tmax ranged from 1 to 4 hours and delayed a little with food.

- **Distribution**

Reference ID: 3072217

Mifepristone is extensively bound to plasma proteins, albumin and α1-acid glycoprotein (AAG). Within the therapeutic dose range, binding to AAG is saturable. The level of AAG showed no correlation with exposure following single dose of 600 mg, while both Ctrough and $AUC_{0\text{-}24hr}$ were highly associated with AAG following multiple doses of 600 mg (n=52), 1200 mg (n=8), and 1800 mg (n=43). The mean apparent volume of distribution (Vd/F) under fed conditions was approximately 270 L.

- **Metabolism of Mifepristone**

According to the Summary of Approval of Mifeprex®, approximately 92% of a radiolabeled dose of 600 mg mifepristone is recovered in the feces, with biliary excretion as the primary route of elimination with 0.5% of the dose being receptor-reactive.

Mifepristone has 6 identified metabolites: M1 (RU 42633, N-desmethyl mifepristone), Mw (RU 42848, N,N-didesmethyl mifepristone), M3 (RU 42698, Hydroxymethyl-mifepristone), M4 (N-desmethyl-hydroxymethyl-mifepristone), M5 (N,N-didesmethyl-bydroxymethyl-mifepristone), M6 (Formyl mifepristone). Metabolism of mifepristone is primarily via N-demethylation and hydroxylation on the 17-propynyl chain. Cytochrome P450 3A4 has been shown to be responsible enzyme for the three major metabolites M1, M2, and M3 (Jang et al., 1996).

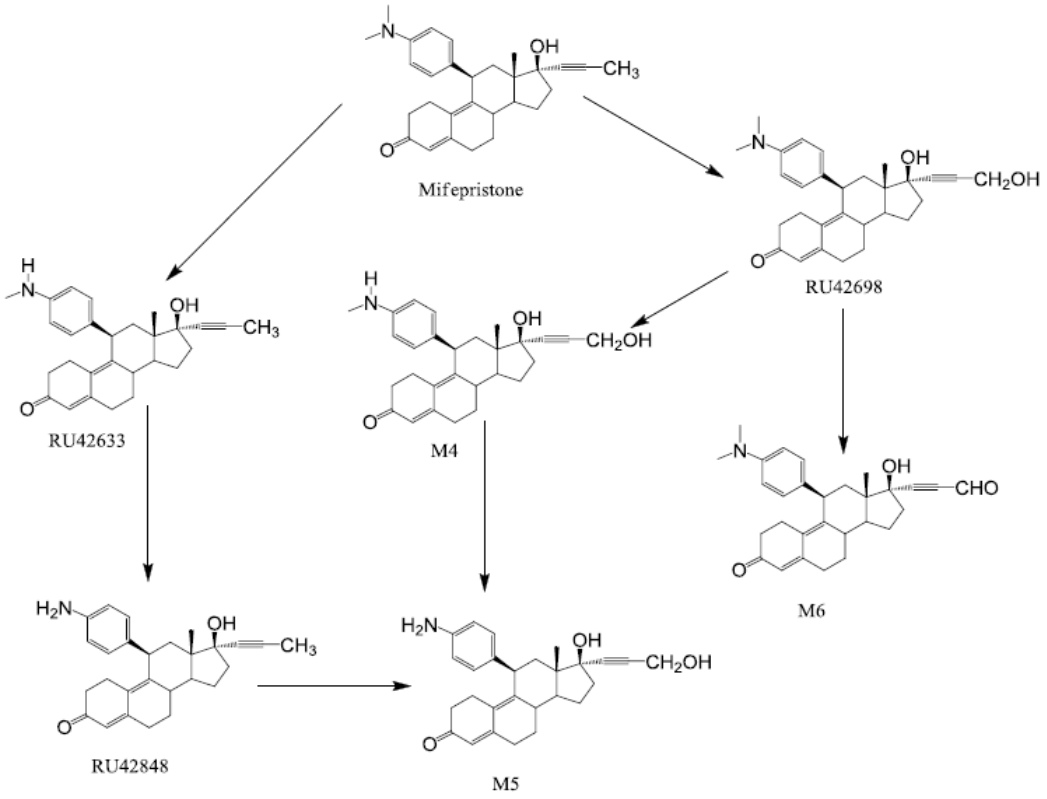


Figure 9. Proposed *in vitro* metabolism of mifepristone in the rat, monkey, and human (ref: Wu et al., 1999)

Reference ID: 3072217

The terminal half-life shows large variability, ranging from 31 to 91 hours following oral administration of single dose ranging 300 mg ~ 1800 mg of mifepristone.

- **Excretion of Mifepristone**

According to the Summary of Approval for Mifeprex, the amount of radiolabeled dose of mifepristone recovered in the feces was about 92%, and excretion in the urine accounts for less than 10% of the dose.

2.2.4.6 Dose mifepristone prolong QT/QTc interval?

The study results are inconclusive. The assay sensitivity was not established as the largest lower bound of the two-sided 90% confidence interval (CI) for the placebo-adjusted, baseline-corrected QTcI (ΔΔQTcI) for moxifloxacin was less than 5 ms. Therefore small changes in QTc interval, defined by ICH E14 guidance, cannot be excluded from the TQT study the sponsor submitted. Refer to QT-IRT review for details.

2.3 Intrinsic factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety response?

2.3.1.1 Hepatic Impairment

Mifepristone was not studied in patients with severe hepatic impairment. Results from the study with moderate hepatic function (Child-Pugh B) did not show evidence for the effect of hepatic function on the pharmacokinetics of mifepristone following 600 mg of mifepristone. However, the upper limit of 90% confidence intervals of AUCs for mifepristone and its metabolites were close to 200% (Table 8).

Although, no difference in pharmacokinetics between healthy volunteers and patients with hepatic impairment was observed, the interpretation should be done with caution. The mechanism-based inhibition might have resulted in significant level of reduction in enzymatic activity in both populations, which might have resulted in insensitivity of detection for the difference. Moreover, nonlinear PK does not allow predictable increase in exposure with dose increase and safety data greater than 1200 mg dose has not been established.

Table 6. Statistical comparison of mifepristone and its metabolites in healthy volunteers and subjects with moderate hepatic impairment following administration of 600 mg mifepristone

Dosing	Analyte	Parameter	GLSM ratio (Impaired/Normal)	90% CI (Impaired/Normal)

Reference ID: 3072217

Multiple Dose 600 mg/day for 7 days	Mifepristone	Cmax	0.92	0.60-1.39
		$AUC_{0\text{-}inf}$	1.02	0.59-1.76
	RU 42633	Cmax	0.71	0.54-0.95
		$AUC_{0\text{-}inf}$	0.95	0.52-1.71
	RU 42698	Cmax	1.06	0.70-1.61
		$AUC_{0\text{-}inf}$	1.37	0.71-2.62
	RU 42848	Cmax	0.55	0.41-0.76
		$AUC_{0\text{-}inf}$	0.62	0.33-1.16

2.3.1.2 Renal Impairment

Results from a study with subjects with severe renal impairment showed no significant change in the pharmacokinetics of mifepristone following administration of 1200 mg of mifepristone. However, the upper limit of 90% confidence intervals of AUCs for mifepristone and its metabolites were all above 200% due to the large variability. The sponsor voluntarily proposed the cap of dose of 600 mg for renal impairment. Due to the lack of dose-exposure relationship (See 2.2.3), and the safety for doses above 1200 mg has not been established, this dosing cap seems reasonable.

Table 7. Statistical comparison of mifepristone and its metabolites in healthy volunteers and subjects with severe renal impairment following administration of 1200 mg mifepristone

Dosing	Analyte	Parameter	GLSM ratio (Impaired/Normal)	90% CI (Impaired/Normal)
Multiple Dose 1200 mg/day for 7 days	Mifepristone	$AUC_{0\text{-}inf}$	1.21	0.71-2.06
		Cmax	1.30	0.97- 1.75
	RU 42633	$AUC_{0\text{-}inf}$	1.43	0.84- 2.44
		Cmax	1.50	1.16,-1.95
	RU 42698	$AUC_{0\text{-}inf}$	1.18	0.64- 2.17
		Cmax	1.33	0.99- 1.80
	RU 42848	$AUC_{0\text{-}inf}$	1.19	0.71- 1.99
		Cmax	1.12	0.87- 1.43

2.3.2 Should dose of mifepristone be adjusted in patients with severe hepatic impairment?

No, but should be avoided. No adjustment of initial dose is recommended to patients with mild/moderate hepatic impairment; however, the maximum dose should be set to 600 mg per day.

The facts that mifepristone is mainly eliminated via metabolism and that its three active metabolites also show prolonged elimination half-lives in patients with moderate hepatic impairment generate concerns for the use of mifepristone in patients with severe impairment. Since linear increase in exposure is not anticipated with dose increase, attempt to match exposure may fail in assurance of efficacy and safety in patients with severe impairment. Thus, mifepristone should not be used in patients with severe hepatic impairment.

Reference ID: 3072217

2.3.3 Should dose of mifepristone be adjusted in patients with renal impairment?

No. Results from a study with subjects with severe renal impairment showed no significant change in the pharmacokinetics of mifepristone following administration of 1200 mg of mifepristone. However, the upper limit of 90% confidence intervals of AUCs for mifepristone and its metabolites were all above 200% due to the large variability. No adjustment of initial mifepristone dose is recommended to subjects with renal impairment. The sponsor has proposed that the maximum dose be limited to 600 mg per day, which is acceptable.

2.3.4 Is there any effect of gender or race on mifepristone PK?

According to the sponsor's analysis for covariates with pre-dose concentrations, race and gender did not affect pharmacokinetics of mifepristone.

2.4 Extrinsic factors

Drug-drug interaction studies are summarized in the Forest plot below.

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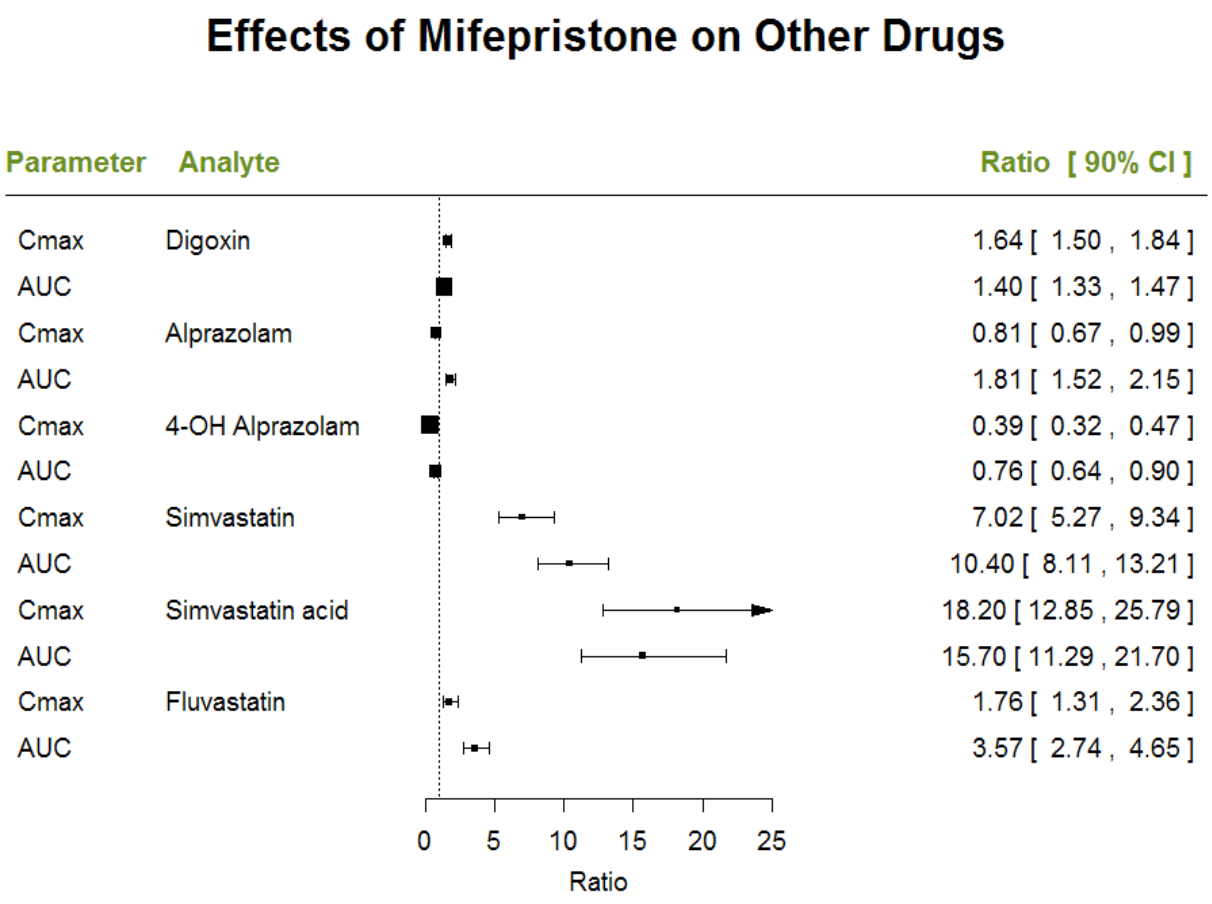

*Simvastatin dose in multiple dosing regimen is 80 mg while 40 mg in single dosing regimen (Exposure was not normalized by dose)

Figure 10. Forest plot for DDI with mifepristone

2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.4.1.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interaction?

Yes. Mifepristone is mainly metabolized by CYP3A4 and its metabolites are substrates of CYP2C8/9. The sponsor's study indicates that mifepristone and its metabolites are inhibitors of various CYP isoforms (See Section 2.5.1.2). In addition, mifepristone is an inhibitor of P-gp and BCRP. Literature reported mifepristone as mechanism-based inhibitor of CYP3A4 and CYP2B6 by covalently binding to their apoproteins (Kan He et al., JPET 1999, Hsia-lien Lin et al, JPET 2009). Furthermore, induction of CYP450 3A has been suggested (J. Andrew Williams et al., DMD 1997).

Reference ID: 3072217

2.4.1.2 Is mifepristone an inhibitor and/or an inducer of enzymes?

Yes, Mifepristone is a strong inhibitor for CYP3A4 and CYP2C9 and moderate inhibitor for CYP2A6 and CYP2C8. Based on the Ki values obtained from *in vitro* studies RU 42633 also seems to have potential for inhibition of CYP2C8 and CYP3A4. The inhibitory potential of RU 42698 for CYP2C9 seems to be significant as well. Only one exception with RU42698 for CYP3A4, all four analytes seems to have substantial potential for CYP2A6 (RU42698), CYP2C8 (mifepristone and RU 42848), CYP2C19 (RU 42698), and CYP3A4 (mifepristone and RU42633).

Table 8. Summary of *in vitro* studies of effect on cytochrome P450

Analyte	Cmax (ng/mL (μM))*	Isoform	Probe	IC_{50} (μM)	[I]/Ki
mifepristone	3329 (7.75)	CYP3A4	Midazolam	9.3	0.52
		CYP2C8	Paclitaxel	8.7	0.43~0.65
RU 42633	2166 (5.21)	CYP3A4	Midazolam	8.6	0.52
		CYP3A4	Testosterone	8.1	0.65~0.87
		CYP2C8	Paclitaxel	3.5	0.74~1.74
RU 42698	832 (1.87)	CYP3A4	Midazolam	8.7	0.08
		CYP2A6	Coumarin	8.5	0.19~0.75
		CYP2C9	Diclofenac	3.0	0.62~1.87
		CYP2C19	S-Mephenytoin	8.5	0.19~0.37
RU 42848	1244 (2.79)	CYP2C8	Paclitaxel	6.7	0.33~0.47

Source: *Cmax from C-1073-05 in healthy subjects

There are studies show that mifepristone is an inducer of various CYP isoforms. *Ex vivo* studies in mice treated with mifepristone as well as *in vitro* studies in cultured mouse hepatocytes demonstrated that there was an increase in the expression of CYP2B mRNA (Jarukamjorn et al., 2001). *In vitro* studies in rat hepatocytes demonstrated that incubation with mifepristone increase CYP3A1/2 mRNA levels (Kocarek et al., 1995). *Ex vivo* studies in rats showed that treatment with mifepristone resulted in a significant increase in hepatic microsomal and mRNA concentrations of CYP3A23, CYP3A1 and CYP3A18 (Cheesman and Reilly, 1998). Incubation of rabbit hepatocytes with mifepristone resulted in increase in CYP3A6 mRNA levels, and incubation of human hepatocytes with mifepristone resulted in increase in CYP3A mRNA levels (Kocarek et al., 1995).

2.4.1.3 Is mifepristone a substrate, an inhibitor and/or an inducer of any relevant transporter?

Yes. Mifepristone is a strong inhibitor of P-glycoprotein (P-gp) with IC_{50} value of 1.8 μM and BCRP with IC_{50} of 5.6 μM. Furthermore, literature studies also support that mifepristone inhibits P-gp (Donald J. Gruol et al., Cancer Research, 1994).

Reference ID: 3072217

Mifepristone also interacted with all the investigated uptake transporters. The most potent inhibition was observed in the cases of OATP1B1 (IC_{50} of 9.1 µM), OATP1B3 (IC_{50} of 1.0) µM and OATP2B1 (IC_{50} of 4.3) µM with IC_{50} in the low micromolar range (< 10 µM). Inhibitory effects were less potent in case of NTCP (IC_{50} of 70 µM) and OCT1 (IC_{50} of 67 µM).

The calculated [I]/Ki indicated that no transporters except P-gp have high potential drug-drug interaction.

2.4.1.4 What are effects of mifepristone on other drugs?

- DDI with simvastatin

Concomitant administration of a single dose of mifepristone 1200 mg/day resulted in an almost 3-fold increase in Cmax and an almost 4-fold increase in $AUC_{0\text{-inf}}$ for simvastatin. Increases in simvastatin acid Cmax and $AUC_{0\text{-inf}}$, were even greater than 9-fold and almost 7-fold, respectively. The sponsor reported that multiple doses of mifepristone 1200 mg/day for 10 days (Day 17) produced a 7- fold increase in Cmax and a greater than 10- fold increase in $AUC_{0\text{-inf}}$ relative to Day 1. Increases in simvastatin acid Cmax and $AUC_{0\text{-inf}}$ were even greater (greater than 18- fold and almost l6-fold, respectively). Furthermore, the sponsor discussed that these increases resulted in simvastatin and simvastatin acid PK parameter increases of approximately 2- to 3- fold for the last dose of mifepristone as compared to the first dose. It should be noted that the dose of simvastatin concomitantly administered with mifepristone on Day 17 was 80 mg while the dose of simvastatin on Day 1 and Day 7 was 40 mg. The sponsor voluntarily contraindicated concomitant use of simvastatin.

Figure 11. Schematic summary of study design for DDI with simvastatin

- DDI with digoxin

The sponsor reported that Cmax values of digoxin were increased when digoxin was administered with the first dose (ratio, 1.68, CI, 1.54-1.84) and the last dose of mifepristone (ratio, 1.64, CI, 1.50-1.79). Digoxin $AUC_{0\text{-}24hr}$ was higher after the last dose

Reference ID: 3072217

of mifepristone as compared to when it was administered alone (ratio 1.40, CI, 1.33-1.47) with loading doses. The sponsor even claimed that AUC_{0-24} was deemed equivalent when digoxin was administered with the first dose of mifepristone compared to alone (ratio 1.19, CI 1.13-1.25).

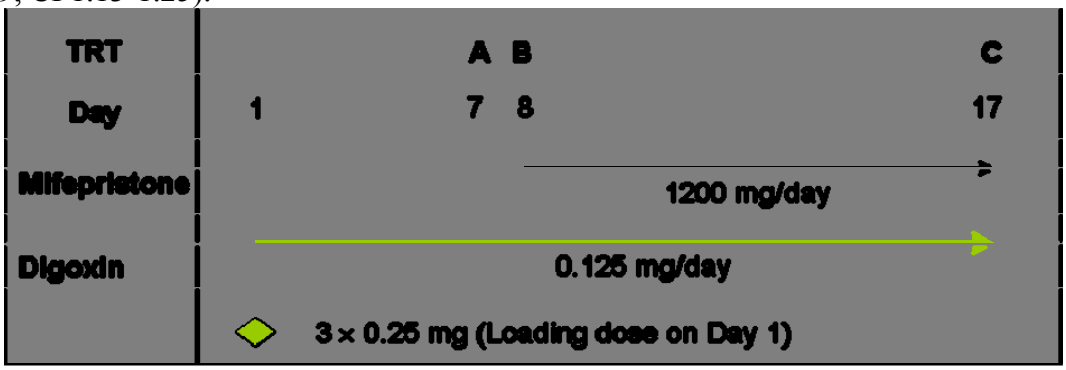

Figure 12. Schematic summary of study design of DDI with digoxin

- DDI with alprazolam

$AUC_{0-72\ hr}$ of alprazolam and 4-OH alprazolam following 1 mg of alprazolam increased 80% (n=16) and 76% (n=16) , respectively with concomitant administration of multiple doses of 1200 mg/day mifepristone for 10 days compared to those following 1 mg of alprazolam alone. AUC_{0-inf} of alprazolam and 4-OH alprazolam following 1 mg of alprazolam increased 67% (n=4) and 94% (n=5), respectively with concomitant administration of multiple doses of 1200 mg/day mifepristone for 10 days compared to those following 1 mg of alprazolam alone. The half-life increase in both alprazolam and 4-OH alprazolam (14.9 hours increase to 37.9 hours and 14.7 hours to 32.8 hours, respectively, with multiple doses of mifepristone) resulted in substantial number of subjects (12 out of 16 subjects) having greater than 25% of extrapolated % for AUC_{0-inf}. Thus, the estimated geometric mean ratios for $AUC_{0-72\ hr}$ for both alprazolam and 4-OH alprazolam do not truly represent the expected drug interaction. Co-administration of mifepristone may increase AUC of both alprazolam and 4-OH alprazolam more than double. Cmax of alprazolam and 4-OH alprazolam following 1 mg of alprazolam decreased by 19% (n=16) and 61% (n=16), respectively with concomitant administration of multiple doses of 1200 mg/day mifepristone for 10 days compared to those following 1 mg of alprazolam alone.

The sponsor proposed CYP3A4 substrates to be administered at the lowest or a reduced dose when used with mifepristone.

It is likely that exposures of sensitive CYP3A substrates (e.g., alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil,) are increased significantly when co-administered with mifepristone. Furthermore, CYP3A substrates with narrow therapeutic window (e.g., alfentanil, astemizole, cisapride, cyclosporine,

Reference ID: 3072217

dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine) may be subject to increased toxicity when co-administed with mifepristone.

Therefore, it is reasonable to avoid sensitive CYP3A substrates and use the lowest dose for other CYP3A substrates when used concomitantly with mifepristone. The use of midazolam should be contraindicated.

Figure 13. Schematic summary of study design of DDI with alprazolam

- DDI with fluvastatin

The first and last multiple doses of mifepristone 1200 mg/day for 7 days produced 2.67-fold and 3.57 fold increase, respectively, in fluvastatin AUC_{0-24}. Single and multiple doses of mifepristone produced equivalent increases in the Cmax of fluvastatin (70% and 76%, respectively). Median Tmax of fluvastatin increased from 0.53 hr to 1.00 hr following a concomitant single dose of mifepristone and increased to 2.04 hr following multiple doses of mifepristone. Mean half-life of fluvastatin increased slightly following the first dose (21 %) and last dose of mifepristone (37%). The results indicate that mifepristone inhibits the metabolism of fluvastatin via CYP2C9 significantly and dose adjustment of fluvastatin and other CYP2C8/9 substrates is necessary. The sponsor proposed the use of smallest recommended doses and close monitor for adverse effects.
It should be noted that fluvastatin is not a sensitive CYP2C8/9 substrate. Regardless, the sponsor's proposal seems acceptable.

Figure 14. Schematic summary of study design of DDI with fluvastatin

Reference ID: 3072217

2.4.1.5 What are the effects of other drugs on mifepristone

- DDI with cimetidine

The geometric least square mean (GLSM) ratio for AUC_{0-24} of mifepristone at steady state following multiple doses of 300 mg/day mifepristone with versus without co-administration of first dose of multiple doses of 800 mg/day cimetidine was 0.91 (CI 0.87-0.94). The geometric least square mean (GLSM) ratio for AUC_{0-24} of mifepristone at steady state with versus without co-administration of first dose of multiple doses of 800 mg/day cimetidine was 0.78 (CI 0.72-0.86). The geometric least square mean (GLSM) ratio for AUC_{0-24} of mifepristone at steady state with versus without co-administration of 7th dose of multiple doses of 800 mg/day cimetidine was 0.85 (CI 0.82-0.88). The geometric least square mean (GLSM) ratio for AUC_{0-24} of mifepristone at steady state with versus without co-administration of 7th dose of multiple doses of 800 mg/day cimetidine was 0.75 (CI 0.69-0.82).

It should be noted that the effect of cimetidine was evaluated at presumably steady state of mifepristone. However, the steady state of mifepristone is not likely achieved by Day 7, thus the drug-drug interaction could be confounded by auto-inhibition of mifepristone on its own.

Nonetheless, there is no evidence for the effect of cimetidine on the pharmacokinetics of multiple doses of mifepristone based on the study results.

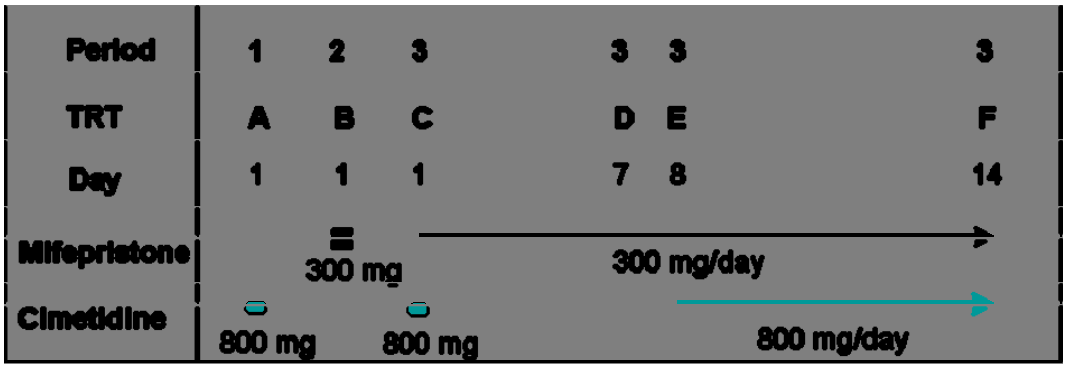

Figure 15. Schematic summary of study design of DDI with cimetidine

2.4.2 Should dose of mifepristone be adjusted with concomitant use of strong, moderate, and mild CYP3A4 inhibitors?

The drug-drug interaction study with cimetidine 800 mg did not show increase in the exposure of mifepristone. Drug-drug interaction study with moderate/strong inhibitors was not conducted to address the effect of CYP3A inhibitors. Nonetheless, increase in the exposure of mifepristone and/or its metabolites are expected with concomitant use of moderate and strong CYP3A4 inhibitors. Use of strong CYP3A4 inhibitors is proposed to be contraindicated by the sponsor. The sponsor recommends no dose adjustment for

Reference ID: 3072217

moderate CYP3A4 inhibitors based on the results from DDI with cimetidine. However, the concomitant administration of moderate CYP3A4 inhibitors should be also avoided until further information is provided.

2.4.3 Are DDI studies with moderate and/or strong CYP3A4 inhibitors needed?

(b) (4)

The significant increase in half-life with multiple doses of mifepristone indicates that mechanism-based inhibition of mifepristone is clearly presented in clinical pharmacokinetic data. Furthermore, *in vitro* studies showed mifepristone inhibits CYP3A4 and CYP2B6 by covalently binding to their apoproteins (Kan He et al., JPET 1999, Hsia-lien Lin et al, JPET 2009).

The Agency recommended a drug-drug interaction study with a strong CYP3A4 inhibitor prior to the submission because the DDI study with a cimetidine, could not adequately address the DDI with CYP3A4 inhibitors. Instead of conducting a DDI study with ketoconazole, the sponsor provided two randomly-timed concentrations of mifepristone obtained from one patient who were on the concomitant use of 400 mg TID ketoconazole during Phase 3 clinical trial on page 122 in Clinical Pharmacology Summary. Those concentrations were 8,520 and 8,770 ng/mL (75 minutes apart between the two samples), which were more than 4 times higher than average trough concentrations (~2,000 ng/mL). However, reasonable interpretation of these concentrations was not possible, because detailed information was not provided further.

(b) (4)

The results obtained from the DDI with cimetidine indicate that the mechanism-based inhibition by mifepristone itself seems to be stronger than any inhibitory effect of cimetidine. The drug interaction was assessed only for the effect of cimetidine on the steady-state PK of mifepristone and did not show any evidence for drug interaction.

Thus, DDI studies to evaluate the inhibitory effects of strong CYP3A4 inhibitor (ketoconazole is recommended) is recommended. Based on the results further evaluation to determine the effect of a moderate CYP3A4 inhibitor on mifepristone pharmacokinetics may be needed.

2.4.4 Should CYP2B6 substrates such as bupropion and efavirenz be avoided?

Reference ID: 3072217

Mifepristone has been reported to be a mechanism-based inhibitor of CYP3A4 and CYP2B6 by covalently binding to their apoproteins (Kan He et al., JPET 1999, Hsia-lien Lin et al., JPET 2009). However, the sponsor's *in vitro* studies do not include any information for mechanism-based inhibition of mifepristone on CYP2B6 and CYP3A4. Furthermore, the sponsor did not choose an adequate inhibitor for CYP2B6 in the submitted *in vitro* study (recommended and acceptable substrates are listed in the following webpage http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm). Since a drastic drug-drug interaction of mifepristone with CYP3A4 substrates such as simvastatin has been observed, drug-drug interaction of mifepristone with CYP2B6 substrates such as bupropion and efavirenz is anticipated. Therefore, concomitant use of mifepristone with bupropion or efavirenz should be avoided.

2.4.5 Should dose of CYP2C8/9 substrates be adjusted or use of CYP3A4 substrates be contraindicated with concomitant use of mifepristone?

Yes. Concomitant administration of mifepristone increased the exposure of fluvastatin significantly The first and last multiple doses of mifepristone 1200 mg/day for 7 days produced 2.67-fold and 3.57 fold increase, respectively, in fluvastatin AUC_{0-24} following administration of single dose of 400 mg fluvastatin. (b) (4)

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system principles, under which category is this drug classified?

From the study C-1073-PK-008 titled "BCS Classification of Test Article Mifepristone: Preliminary Caco-2 Permeability Study", mean (SD) solubility of mifepristone in the Hanks Balanced Salt Solution containing 10 mM HEPES and 15 mM glucose at pH 7.4 was 0.613 (0.08) µM. The permeability of mifepristone was assessed with pindolol (10 µM) and atenolol (100 µM) as low and high permeability controls, respectively. Mean (SD) mifepristone apparent permeabilities (Papp) for A-to-B and B-to-A directions were 28.9 (1.28) and 51.6 (3.23) $\times 10^{-6}$ cm/s, respectively. The ratio (B/A) was 1.79. The Papp (A-to-B) value for mifepristone was numerically larger than that of pindolol, 28.9 (1.28) versus 19.4 (0.415) $\times 10^{-6}$ cm/s, respectively.

Based on this study, the sponsor claims mifepristone could be considered as Class 2 drug under BCS (Biopharmaceutical Classification System). However, the study was a preliminary study, which was not conducted in compliance with Good Laboratory

Reference ID: 3072217

Practice (GLP) regulations, and the results were preliminary as the report [redacted] (b) (4) clarified. BCS guidance recommends that permeability studies be performed at concentrations equivalent to 1, 0.1, and 0.01 times the highest dose strength in humans dissolved in 250 mL. However, the study was conducted with only once concentration (0.5 μM, which is 0.00018 times of the 300 mg dose strength) due to the low solubility of mifepristone.

2.5.2 What are protein-binding properties of the drug?

Mifepristone is believed to be highly bound to α1-acid glycoprotein (AAG) and approaches saturation at doses of 100 mg (2.5 μM) or more. Mifepristone and its metabolites also bind to albumin and distribute to other tissues, including the central nervous system.
Form equilibrium dialysis studies, the fraction of protein binding were found to be 99.2% for mifepristone, 98.9% for RU 42633, 97.8% for RU 42698, and 96.1% for RU 42848. These values were from experiments for one analyte. The protein binding of mifepristone in the presence of its metabolites and vice versa was not studies *in vitro*. Study C-1073-PK-002 included concentrations of 0.2, 1, 5, and 10 μg/mL, and 1 and 5 μg/mL are representative concentrations for the clinical doses.

2.5.2.1 What is the effect of food on pharmacokinetics of mifepristone and its metabolites?

Three food effect studies were conducted by the sponsor with 1200 mg single dose, 1200 mg multiple doses, and 600 mg single dose. Food increase Cmax of mifepristone by 19% and AUC by 29% following a single dose of 600 mg of mifepristone. Similar food effects were observed for metabolites. With a single dose administration of 1200 mg of mifepristone, a high-fat, high-calorie breakfast increased mifepristone Cmax and $AUC_{0\text{-inf}}$ by 29% and 42%, respectively, with increase for the metabolites ranging from 9 to 32% for Cmax and from 34% to 51% for $AUC_{0\text{-inf}}$. While mifepristone was administered with multiple doses of 1200 mg/day, mean Cmax and $AUC_{0\text{-24hr}}$ of mifepristone increased ~ 32% and 43%, respectively, after the first dose of 1200 mg mifepristone and 56% and 65%, respectively, after 7 days of mifepristone 1200 mg/day under fed conditions (34% fat breakfast) compared with fasting condition. After an eighth day of dosing with mifepristone 1200 mg/day given with a 50% fat breakfast, Cmax and $AUC_{0\text{-24hr}}$ increased by 52% and 68%, respectively, compared with fasting condition. Cmax and $AUC_{0\text{-24hr}}$ following mifepristone dose with 50% fat meal were similar to those with 34% fat breakfast. The food delayed drug absorption and reduced the interindividual variability in pharmacokinetic parameters. Furthermore, the less-than-proportional increase in exposure, which is limited by the low solubility of mifepristone, seems to be closer to proportional with food at doses higher than 600 mg. The food effect was not dependent on the meal content. According to the sponsor's proposed labeling, mifepristone is recommended to be taken with food that is in accordance with the dosing scheme used in the Phase 3 trial.

Reference ID: 3072217

2.6 Analytical Section

2.6.1 What bioanalytical methods are used to assess the drug concentrations?

Concentrations of plasma samples for mifepristone and its three active metabolites, RU 42633, RU 42698, RU 42848 were determined by high-performance liquid chromatography (HPLC) with mass spectrometric (MS/MS) detection. The internal standards for the analyses were d_4-mifepristone, d_4-RU 42633, d_4-RU 42698, d_4-RU 42848. The lower limit of quantification was 10 ng/mL for each analyte on a calibration curve from 10 to 2000 ng/mL.

One validation run containing a single calibration curve, five QC samples at each concentration level (30.0, 300.0 and 1600.0 ng/mL), one reagent blank, one plasma blank and one control zero were analyzed. For recovery, five additional plasma blanks were extracted in the intraday validation run. Five replicates of internal standard (5.00 µg/mL) were spiked post extraction and the mean of the peak heights was compared to the peak height mean of the internal standards spiked in the QC samples for recovery determination. For matrix effect, three replicates each of six blank plasma lots were spiked with a target concentration of 100.0 ng/mL and extracted with one of the validation runs.

The accuracy of the analytical method was determined by comparing the mean of the measured concentrations of the analytes in the QC samples with the actual values. The deviation from the actual values of the plasma standards did not exceed ±4.0%, ±5.0%, ±3.0% and ±6.3% for any concentration level of mifepristone, RU 42633, RU 42698 and RU 42848. The intraday mean values ranged from 1.3% to 6.1% deviation for mifepristone, 1.7% to 3.7% for RU 42633, -1.0% to 3.3% deviation for RU 42698 and -1.9% to 10.0% for RU 42848 from the actual values for the QC samples concentrations.
The precision of the analytical method was measured from three QC sample concentrations with each analytical run. The %CV for mifepristone, RU 42633, RU 42698 and RU 42848 in the QC samples did not exceed 4.1%, 1.9% 3.0% and 7.8%, respectively. The intraday precision was 1.4%, 1.8%, and 3.3% for the samples of 30.0 ng/mL, 300.0 ng/mL 1600 ng/mL, respectively.

The recoveries of d_4-mifepristone, d_4-RU 42633, d_4-RU 42698, d_4-RU 42848 were determined by comparing the peak heights of extracted internal standards spiked into QC samples with the peak heights of unextracted recovery internal standards spiked into extracted blank plasma at the same concentrations. The overall mean recoveries of d_4-mifepristone, d_4-RU 42633, d_4-RU 42698, d_4-RU 42848 were 98.1%, 143.4%, 103.9%, 144.1%, respectively.

Reviewer's comments: Long-term stability in biological matrix has not been assessed (the sponsor indicated those studies are ongoing and planning to update when available). However, QC samples for stability (thawed at room temperature) for 24 hours, QC samples for storage stability (frozen at -20°C) for 89 days, QC samples for storage

Reference ID: 3072217

stability (freeze/thaw) for 3 cycles, and extracted samples for processed sample stability (reinjection) at room temperature for 73 hours showed less than 15% deviation from theoretical values. Moreover, mifepristone and its 3 metabolites are believed to be stable at 25°C/60%RH condition for 36 months according to the stability study and according to CMC's review team (per discussion with Dr. Suong Tran).

Reference:

Gross BA et al., "Medical Management of Cushing Disease," Neurosurgical Focus; 23(3): E10 (2007)

Kan He et al., "Mechanism-base Inactivation of Cytochrome P-450-3A4 by Mifepristone (RU486), The Journal of Pharmacology and Experimental Therapeutics 288(2): 791-797 (1999)

Heikinheimo O. "Pharmacokinetics of the Antiprogesterone RU 486 in Women During Multiple Dose Administration". J Steroid Biochem 1989; 32:21-25.

Jang GR et al., "Identification of CYP3A4 as the principal enzyme catalyzing mifepristone (RU 486) oxidation in human liver microsomes.", Biochem Pharmcol; 52(5):753-761 (1996)

Hsia-lien Lin et al., "Metabolic Activation of Mifepristone [RU486; 17β-Hydroxy-11β-(4-dimethylaminophenyl)-17α-(1-propynyl)-estra-4,9-dien-3-one] by Mammalian Cytochrome P450 and the Mechanism-Based Inactivation of Human CYP2B6"; 329(1): 26-37 (2009)

Shi YE et al., "Pharmacokinetic Study of RU 486 and Its Metabolites after Oral Administration of Single Doses to Pregnant and Mon-pregnant Women"; 48(2): 133-49 (1993)

Williams JA et al., "Induction of Cytochrome P4503A by the Antiglucocorticoid Mifepristone and a Novel Hypocholesterolaemic Drug," Drug Metabolism and Disposition 25(6): 757-761 (1997)

3 Labeling

Detailed labeling comments will be included in the addendum to Clinical Pharmacology review.

4 Appendix

4.1 Individual Clinical Study Review

Reference ID: 3072217

4.1.1 C-1073-05: Effect of Hepatic Impairment Study with Subjects with Child-Pugh B

Title: Phase 1 Study of the Pharmacokinetics of Single and Multiple Doses of C-1073 (Mifepristone) in Hepatically-impaired Subjects as Compared to Healthy Volunteers

<table>
<tr><td>Objectives</td><td>Primary:
• To evaluate the safety and pharmacokinetic properties of single and multiple doses of mifepristone in subjects with moderate liver impairment (Child-Pugh B) as compared to matched healthy volunteer controls</td></tr>
<tr><td>Study Design</td><td>This was a 2-period, open-label study in subjects with moderate hepatic impairment and in healthy volunteers. The first period evaluated a single dose of mifepristone 600 mg, while the second period evaluated multiple doses of mifepristone 600 mg/day for 7 days. The volunteers were matched to the hepatically-impaired subjects according to age (± 5 years), weight (± 10%), gender and smoking status ("nonsmoker" was defined as anyone who has not smoked for at least 6 months). Following both the single dose and the seventh multiple dose of mifepristone, serial blood sampling was performed over 2 weeks for determination of mifepristone and its 3 active metabolites (RU 42633, RU 42698, RU 42848). Subjects were dosed after an overnight fast; breakfast was served approximately 2 hours after dosing. Final safety evaluations were also performed at the time of the last pharmacokinetic sample.</td></tr>
<tr><td>Study population</td><td>Ten subjects with moderate hepatic impairment and 10 healthy volunteers</td></tr>
<tr><td>Treatments</td><td><table><tr><th>Day</th><th>Period</th><th>Mifepristone</th></tr><tr><td>1</td><td>1</td><td>600 mg SD</td></tr><tr><td>7</td><td>2</td><td>600 mg/day</td></tr><tr><td>15</td><td>2</td><td>600 mg/day</td></tr></table></td></tr>
<tr><td></td><td></td></tr>
<tr><td>PK Assessment</td><td>Blood sampling for plasma PK analysis was taken within 15 minutes prior to dose and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 15, 24, 48, 72, 96, 144, 240, and 336 hours post-dose in both periods. In addition, blood samples were taken during multiple dose administration prior to the first, second, fifth and sixth doses. [redacted] (b) (4) assayed all plasma samples for mifepristone and the 3 active metabolites (RU 42633, RU 42698 and RU 42848) using a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) assay method. The lower limit of detection of this method was 10 ng/mL for each analyte.
Pharmacokinetic parameters calculated included Tmax, Cmax, AUC_{0-24}, AUC_{0-last} (Period 1 only), AUC_{0-inf} (Period 1 only), $T_{1/2}$, CL/F (Period 1</td></tr>
</table>

Reference ID: 3072217

	only), V/F (Period 1 only), and accumulation ratio. Statistical comparisons of pharmacokinetic parameters in the two populations were performed using 90% confidence intervals. Equivalence was determined if CIs were contained within 0.80-1.25.
Safety Assessment	Safety assessments included monitoring of adverse events (AEs), clinical laboratory, vital sign measurements, physical examinations, and 12-lead electrocardiograms (ECGs).

Results:

Safety: No deaths, serious adverse events, early terminations, or interruptions in dosing were reported in this pharmacokinetic study in all subjects. The most common adverse event reported was mild headache, reported by 9 of 20 subjects (45%), and often observed in confinement studies. One subject with hepatic impairment experienced moderately severe orthostatic hypotension of 24 hours duration.

PK: Mean (SE) concentration vs. time profiles of mifepristone and its metabolites are shown in Figure 16 and their pharmacokinetic parameters are summarized in Table 11. Following both single dose and multiple doses of 600 mg of mifepristone, plasma concentrations of mifepristone, RU42633 (mono-demethylated metabolite) and RU42698 (mono-hydroxylated metabolite) rose quickly while concentrations of RU42698 (di-demethylated metabolite) rose slower. The distribution and elimination characteristics of mifepristone and its metabolites seem to be similar between subjects with moderate hepatic impairment and healthy subjects.

Reference ID: 3072217

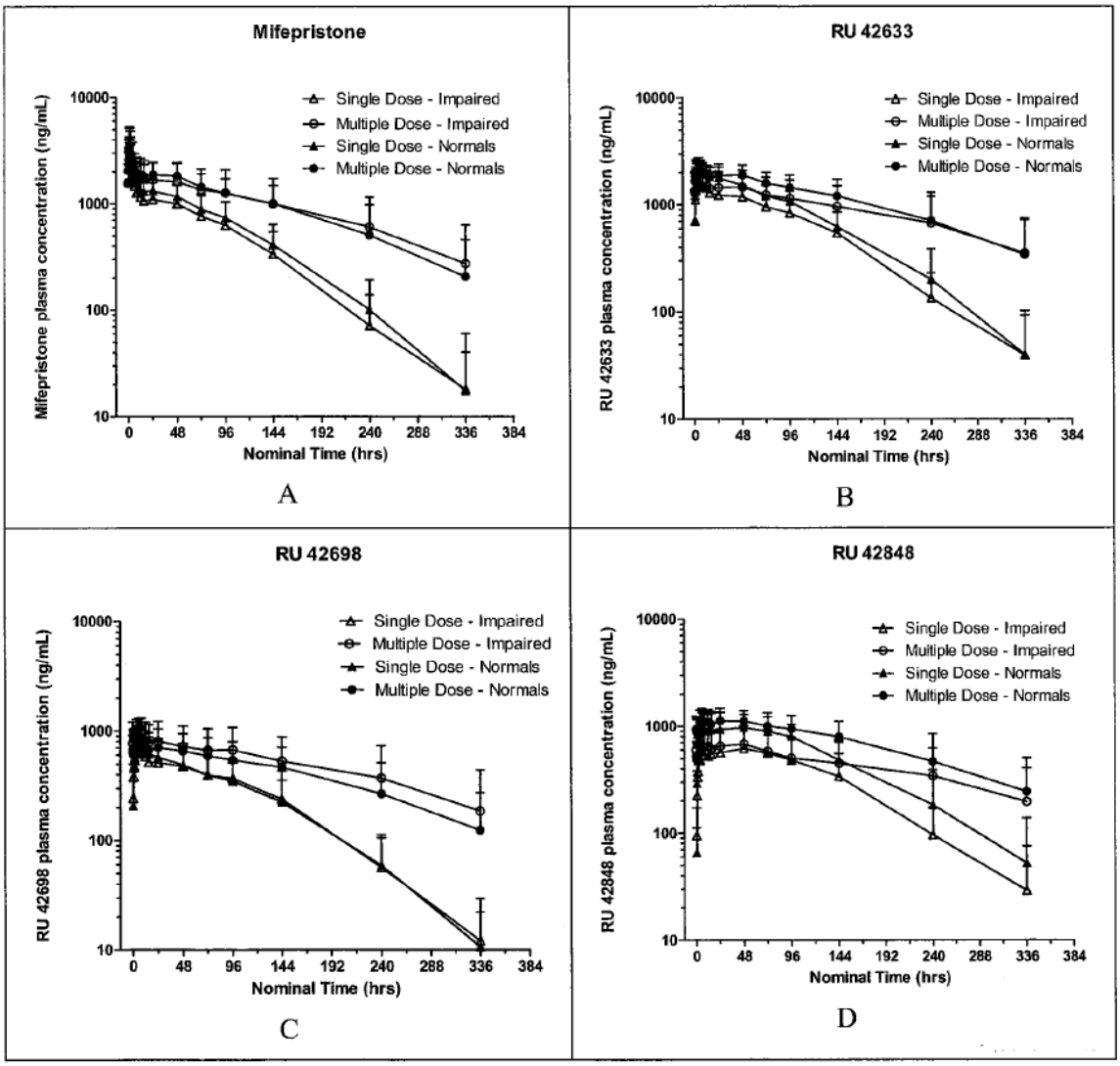

Figure 16. Mean (SE) Plasma concentrations of mifepristone and its metabolites following single (600 mg) and multiple doses (600 mg/day for 7 days) of mifepristone

Table 9. Pharmacokinetics parameters of mifepristone and its metabolites following single (600 mg) and multiple doses (600 mg/day for 7 days) of mifepristone

Single Dose					
Hepatic Function	**Analyte**	**Tmax (hr)**	**Cmax (ng/mL)**	**$AUC_{0\text{-}inf}$ (ng*hr/mL)**	**T1/2 (hr)**
Impaired (n=10)	Mifepristone	1.7±1.6	2648±1785	143383+76384	42.6+25.9
	RU 42633	8.5+6.5	1648±909	188762±102142	52.7±39.2
	RU 42698	10.6±13.5	719±432	78330±54913	52.9±28.6
	RU 42848	43.1±24.3	680±369	105003±62189	61.8±48.1
Normal (N=10)	Mifepristone	1.9±1.8	2982±1040	170331±61681	43.0±14.5
	RU 42633	14.0±1.5	2331±456	240216±82136	44.5±14.7
	RU 42698	9.6±13.7	804±291	79591±37437	47.9±13.5
	RU 42848	35.1±28.1	1077±377	167721±70314	54.4±26.8

Reference ID: 3072217

Multiple Dose					
Hepatic Function	**Analyte**	**Tmax (hr)**	**Cmax (ng/mL)**	**AUC $_{0-24}$ (ng*hr/mL)**	**T1/2 (hr)**
Impaired (n=10)	Mifepristone	2.4±2.5	3398±2123	46074+23144	78.0+44.4
	RU 42633	11.7+14.8	1655±722	34267±14495	67.5±26.0
	RU 42698	16.7±28.1	916±486	18979±9548	117±96.0
	RU 42848	51.4±70.1	726±332	14493±6254	72.7±29.8
Normal (N=10)	Mifepristone	1.1±0.6	3329±1260	48020±14358	71.6±45.4
	RU 42633	9.0±13.8	2166±480	45008±10354	100±82.6
	RU 42698	7.0±6.2	832±362	16685±7253	75.3±42.9
	RU 42848	24.4±21.1	1244±368	25265±7525	90.2±64.2

Reviewer's comments: The major metabolites are expected to be decreased in hepatic impairment but interestingly significant decrease in the exposure of parent compound along with decrease in the exposure of metabolites was observed.

Notable change in half-lives in multiple-dose PK compared to single-dose PK. The parallel decrease of metabolites indicates that the metabolism kinetics is formation-rate limited.

Table 10. Statistical comparisons of pharmacokinetic parameters of mifepristone and its metabolites in subjects with normal or moderate hepatic impairment

Dosing	**Analyte**	**Parameter**	**GMLS ratio (Impaired/Normal)**	**90% CI (Impaired/Normal)**
Single Dose 600 mg	Mifepristone	Cmax	0.77	0.51-1.27
		AUC_{inf}	0.79	0.53-1.16
	RU 42633	Cmax	0.62	0.47-0.95
		AUC_{inf}	0.71	0.49-1.09
	RU 42698	Cmax	0.80	0.54-1.25
		AUC_{inf}	0.90	0.53-1.44
	RU 42848	Cmax	0.58	0.36-0.90
		AUC_{inf}	0.57	0.32-0.93
Multiple Dose 600 mg/day for 7 days	Mifepristone	Cmax	0.92	0.61-1.43
		AUC_{0-24h}	0.90	0.65-1.27
	RU 42633	Cmax	0.71	0.55-0.98
		AUC_{0-24h}	0.71	0.54-0.98
	RU 42698	Cmax	1.06	0.70-1.50
		AUC_{0-24h}	1.09	0.73-1.52
	RU 42848	Cmax	0.55	0.37-0.80
		AUC_{0-24h}	0.55	0.36-0.79

Accumulation: The sponsor reported the accumulation ratio for the four analytes were 1.05~1.45 in healthy subjects and 1.18~1.59 for hepatic impairment, respectively.

Table 11. Accumulation ratio for mifepristone and its metabolites in subjects with normal or moderate hepatic function

Hepatic function	**Mifepristone**	**RU 42633**	**RU 42698**	**RU 42848**
Impaired	1.52±0.36	1.18±0.33	1.59±0.58	1.41±0.46
Normal	1.31±0.23	1.05±0.31	1.12±0.27	1.45±0.65

Reference ID: 3072217

Reviewer analysis and comments: The accumulation ratio cannot be a simple ratio of Cmax following single-dose and multiple-dose when drug elimination is prolonged (e.g., prolonged half-life due to saturated metabolism or suicidal inhibition). As seen in Table 11, there are significant increases in half-lives for all analytes. Theoretically, the accumulation ratio for mifepristone is to be 2.59 when half-life does not change with multiple dosing. With the increase half-life of mifepristone, the accumulation ratio would be approximately 4.3 after 7 days of multiple dosing. Therefore, the accumulation ratio is expected to be between 2.59 and 4.3 following multiple doses of 600 mg/day.

Therefore, the reviewer conducted non-compartmental analysis and the resulting values in comparison of PK parameters of healthy and hepatic impairment are reported in Table 14.

Table 12. Pharmacokinetic parameters for mifepristone and its metabolites following single (600 mg) and multiple doses (600 mg/day for 7 days) of mifepristone (Reviewer's analysis)

Dosing	Analyte	Parameter	GMLS ratio (Impaired/Normal)	90% CI (Impaired/Normal)
Single Dose 600 mg	Mifepristone	Cmax	0.77	0.52-1.14
		AUCinf	0.79	0.51-1.24
	RU 42633	Cmax	0.62	0.45-0.87
		AUCinf	0.71	0.48-1.05
	RU 42698	Cmax	0.80	0.54-1.20
		AUCinf	0.90	0.51-1.57
	RU 42848	Cmax	0.58	0.40-0.85
		AUCinf	0.57	0.37-0.89
Multiple Dose 600 mg/day for 7 days	Mifepristone	Cmax	0.92	0.60-1.39
		AUCinf	1.02	0.59-1.76
	RU 42633	Cmax	0.71	0.54-0.95
		AUCinf	0.95	0.52-1.71
	RU 42698	Cmax	1.06	0.70-1.61
		AUCinf	1.37	0.71-2.62
	RU 42848	Cmax	0.55	0.41-0.76
		AUCinf	0.62	0.33-1.16

Time-dependent pharmacokinetics of mifepristone and its metabolites have been observed from PK profiles of them. The reviewer conducted a separate analysis to describe the time-dependent PK and the results are described in Table 15.

Table 13. Statistical comparisons of pharmacokinetic parameters of mifepristone and its metabolites (Reviewer's analysis)

Population	Analyte	Parameter	GMLS ratio (MD/SD)	90% CI (MD/SD)
Healthy Volunteers (n=10)	Mifepristone	Cmax	1.09	0.89-1.33
		AUCinf	2.03	1.61-2.56
		Half-life	1.79	1.29-2.48
	RU 42633	Cmax	0.93	0.81-1.06
		AUCinf	1.76	1.38-2.25
		Half-life	2.03	1.44-2.88
	RU 42698	Cmax	1.00	0.87-1.15
		AUCinf	1.97	1.57-2.48

Reference ID: 3072217

		Half-life	1.76	1.23-2.53
	RU 42848	Cmax	1.18	1.02-1.37
		AUCinf	1.72	1.30-2.28
		Half-life	1.91	1.40-2.62
Hepatic Impairment (n=10)	Mifepristone	Cmax	1.30	1.15-1.46
		AUCinf	2.60	2.05-3.30
		Half-life	2.38	1.81-3.14
	RU 42633	Cmax	1.05	0.89-1.24
		AUCinf	2.36	1.73-3.22
		Half-life	2.77	1.66-4.62
	RU 42698	Cmax	1.32	1.08-1.63
		AUCinf	3.01	2.13-4.25
		Half-life	2.46	1.59-3.81
	RU 42848	Cmax	1.12	0.99-1.27
		AUCinf	1.91	1.38-2.64
		Half-life	2.10	1.12-3.95

As seen in Table 15, half-lives of mifepristone and its metabolites in both healthy volunteers and hepatic impairment are increasing with time as daily doses of mifepristone 600 mg are administered. The time-dependent PK presented in both healthy subjects and subjects with moderate hepatic impairment similarly. Consequently, the difference between the pharmacokinetic characteristics in the two populations became insignificant. No dose adjustment is recommended to subjects with mild and moderate hepatic impairment, however, the upper limits of confidence interval for the ratio of $AUC_{0\text{-}inf}$ were over 260% or close 200%, and the studied dose was 600 mg. Thus, the maximum dose should not exceed 600 mg per day.

4.1.2 C-1073-19: Effect of Renal Impairment Study

Title: A Phase 1, Open-Label, Adaptive Two-Stage Study of the Effects of Renal Impairment on the Pharmacokinetics of CORLUX and its Active Metabolites Following Multiple Doses of CORLUX (mifepristone) in Volunteers with Impaired and Normal Renal Function

Objectives	Primary: • To determine the effect of renal function on the pharmacokinetics of mifepristone and its metabolites following multiple doses of mifepristone (1200 mg/day for 7 days)
Study Design	This was an open-label, adaptive two-stage study. The first stage evaluated the effects of severe renal impairment (GFR < 30 mL/min/1.73 m^2 but not on dialysis) as compared to normal renal function (CrCL ≥ 90 mL/min/1.73 m2) on the pharmacokinetics of mifepristone and its three active metabolites RU 42633, RU 42698, RU 42848 following mifepristone 1200 mg/day for 7 days. The second stage of the study is designed to evaluate subjects with mild impairment (CrCL 60~89 mL/min/1.73 m^2) and moderate impairment (GFR 30~59 mL/min/l.73 m^2). Results from Stage 1 are presented here;

Reference ID: 3072217

	Stage 2 has not been conducted. Serial blood sampling over 14 days (normal renal function) and over 28 days (renal impairment) was obtained following the last dose on Day 7. Trough samples were obtained during dosing to determine if steady-state conditions were achieved. A final safety evaluation was performed 2 weeks after the last PK blood sample.
Study population	Eighteen volunteers were enrolled the study: 10 subjects with ESRD but not on dialysis (5 males, 5 females) and 8 healthy subjects with normal function (4 males, 4 females). Mean age was 56.5 (range 35~78) for the ESRD subjects and 36.0 years (range 22~49) for the healthy subjects.
Treatment group	Mean (SD) creatinine clearance by treatment group is described in the table below.

	Renal Function Group	
	Normal (N = 8)	**Severe Impairm (N = 10)**
Measured[a]	83.3 (20.9)	23.5 (8.4)
Cockcroft-Gault[b]	99.3 (3.8)	24.8 (4.8)
MDRD[c]	87.6 (5.4)	21.2 (5.6)

PK Assessment	GFR was determined using 3 methods: (1) measured urine and serum creatinine on Day 1, (2) estimated using Cockcroft-Gault equation adjusted for body surface area and (3) estimated using the modified diet in renal disease (MDRD) equation which includes a correction for body surface area. Serial blood sampling for determination of mifepristone and its metabolites was performed prior to the last mifepristone dose on Day 7 at 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 120, 192, 264, and 336 hours (14 days), 432, 552 and 672 hours (28 days) post-last dose with samples for the latter 3 time points only obtained for subjects with end stage renal disease (ESRD). Pre-dose blood samples were obtained on Days 1, 5, 6 and 7. Unbound (free) concentrations of mifepristone and its primary metabolite, RU 42633, were determined on Day 7 from blood samples collected at 0,2 and 8 h. Total plasma concentrations of mifepristone and its metabolites (RU 42633, RU 42698, and RU 42848) were determined by [redacted] (b) (4) using a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) assay. The lower limit of detection of this method was 10 ng/mL for each analyte. Unbound concentrations of mifepristone and RU 42633 were determined using equilibrium dialysis (a non-GLP assay) with a limit of detection 0.200 ng/mL for both analytes. Total plasma concentrations of mifepristone and its metabolites were used to determine pharmacokinetic parameters Cmax, Tmax, AUC_{0-24}, CL/F, and $T_{½}$, while unbound concentrations of mifepristone and RU 42663 were used to calculate Cmax free, T max, AUC_{0-24} free drug, fu, CL/F for free drug and $T_{½}$. An analysis of variance (ANOVA) was performed to compare PK parameters of the severe renal function group with those of the normal renal function group. The analysis was performed on log (Cmax), log (AUC), and

Reference ID: 3072217

	$T_{½}$ values with group as fixed effect and subject as random effect. The 90% CI for the ratio (severe/normal) of the PK parameters were generated. Equivalence was determined if the 90% CI of the ratio was entirely contained within 0.80-1.25. Median Tmax of mifepristone, RU 42633, RU 42698, and RU 42848 from the severe renal function group was compared to those from the normal renal function group using nonparametric Wilcoxon Rank-Sum test. A P-value of ~ 0.05 provided evidence that the two medians significantly differed. A comparison of mean total and free plasma concentration between normal and severe renal impaired subjects was statistically tested at each scheduled time point using two-sample t-test for mifepristone, RU 42633, RU 42698 and RU 42848 with the differences between the means, 95% CIs and corresponding P-values determined at each scheduled time point. The association between PK parameters and renal function (GFR) was presented using scatter plots for each of the two renal function groups. Total Cmax and AUC_{0-24} and unbound Cmax and AUC_{0-24} for mifepristone were plotted as a function of GFR estimated by all three methods. For the metabolites, total Cmax and AUC_{0-24} and unbound Cmax and AUC_{0-24} (RU 42633 only) were plotted as a function of GFR as determined by measured creatinine clearance. Regression analyses were performed for selected comparisons based on visual inspection of the scatter plots. Measured unbound plasma concentrations of mifepristone and RU 42633 were compared to predicted concentrations.
Safety Assessment	Safety assessments included monitoring of adverse events (AEs), clinical laboratory tests, vital sign measurements, physical examinations, and 12-lead electrocardiograms (ECGs).

Results:

Plasma concentrations of mifepristone and its metabolites for the two treatment groups are described in Figure 17 and pharmacokinetics parameters in these groups following 1200 mg of mifepristone are summarized in Table 16.

Table 14. Pharmacokinetic parameters from total concentrations of mifepristone and its metabolites following mifepristone 1200 mg /day for 7 days

Renal Function	Analyte	T_{max} median (h)	C_{max} (ng/mL)	AUC_{0-24} (ng*h/mL)	$t_{½}$ (h)
Severely Impaired (N = 10)	Mifepristone	1.0	4019 ± 1240	60115 ± 22422	38.4 ± 15.6
	RU 42633	5.0	2493 ± 804	53428 ± 18408	36.4 ± 9.7
	RU 42698	5.0	905 ± 307	18667 ± 6647	45.2 ± 16.3
	RU 42848	36.0	1462 ± 423	30554 ± 9800	42.5 ± 15.0
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

Reference ID: 3072217

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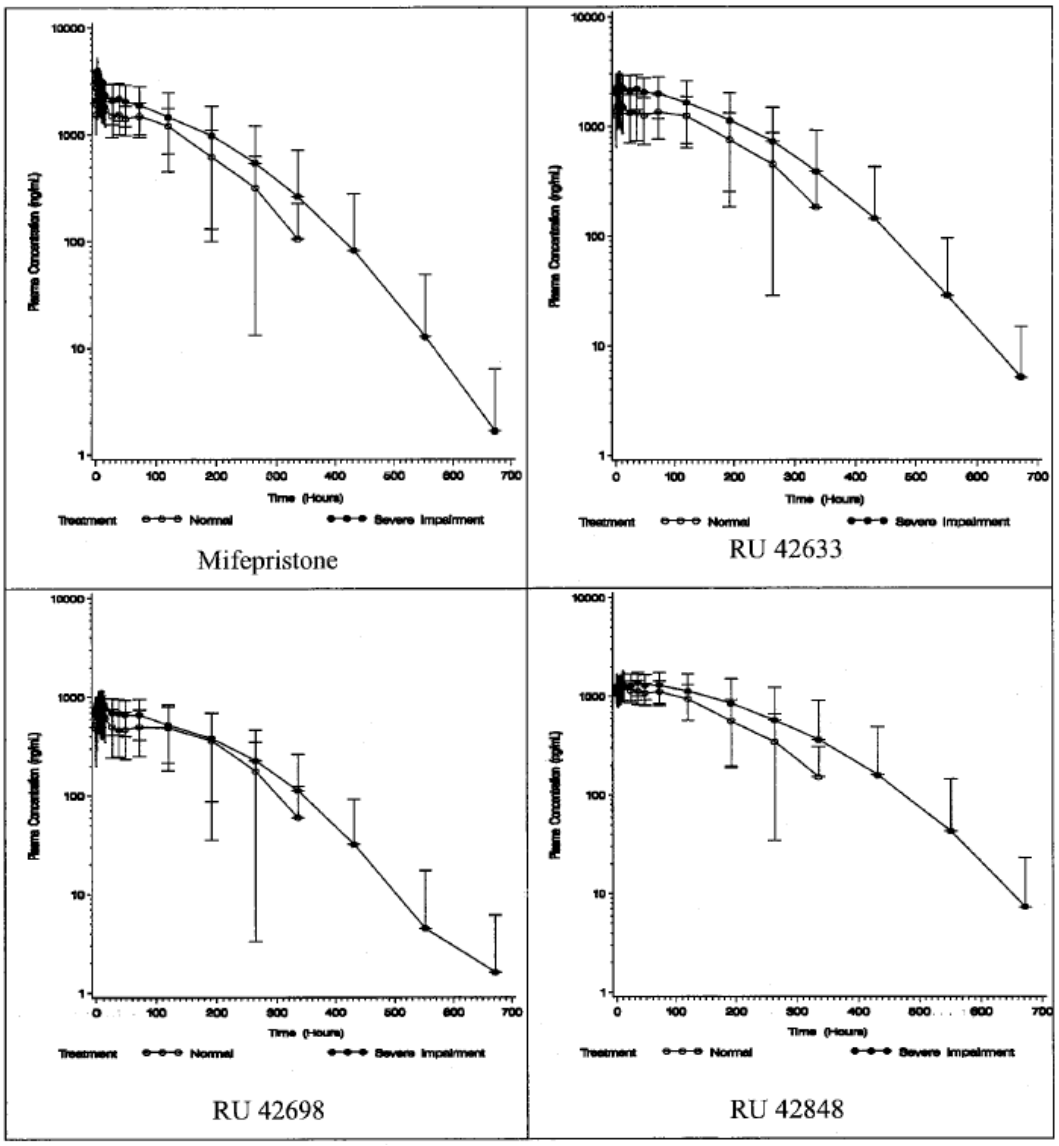


Figure 17. Mean (SE) plasma concentrations of mifepristone and its metabolites following multiple doses of 1200 mg/day for 7 days of mifepristone

Table 15. Pharmacokinetic parameters from unbound concentrations of mifepristone and its metabolites following 1200 mg/day for 7 days

Renal Function	Analyte	C_{max} (ng/mL)	AUC_{0-24} (ng*h/mL)
Severely Impaired (N = 10)	Mifepristone	15.72 ± 9.44	211.4 ± 101.7
	RU 42633	13.89 ± 4.90	294.0 ± 110.0
Normal (N = 8)	Mifepristone	14.15 ± 10.1	169.5 ± 70.5
	RU 42633	14.51 ± 8.51	242.9 ± 104.7

Reference ID: 3072217

The statistical analysis for the pharmacokinetic parameters of mifepristone and its metabolites between subjects with normal or severe renal impairment is summarized in Table 18.

Table 16. Statistical analysis for mifepristone and its metabolites (N=8 in each group)

Analyte	Parameter	Renal Function Group	Geometric Mean	Ratio of Geometric Means [a] (Impair/Normal)	90% CI (Impair/Normal)
Mifepristone	AUC_{0-24} (ng•h/mL)	impaired	56839.1	1.31	(0.99, 1.74)
		normal	43277.5		
	$AUC_{0-24, free}$ (ng•h/mL)	impaired	190.2	1.19	(0.81, 1.76)
		normal	159.3		
	C_{max} (ng/mL)	impaired	3841.5	1.30	(0.97, 1.75)
		normal	2950.7		
	$C_{max, free}$ (ng/mL)	impaired	13.4	1.12	(0.67, 1.88)
		normal	12.0		
	$t_{1/2}$ (h)	impaired	35.9	0.82	(0.54, 1.25)
		normal	43.6 [a]		
RU 42633	AUC_{0-24} (ng•h/mL)	impaired	51223.8	1.56	(1.17, 2.09)
		normal	32760.3		
	$AUC_{0-24, free}$ (ng•h/mL)	impaired	272.7	1.21	(0.83, 1.75)
		normal	225.6		
	C_{max} (ng/mL)	impaired	2398.2	1.50	(1.16, 1.95)
		normal	1594.4		
	$C_{max, free}$ (ng/mL)	impaired	13.1	1.04	(0.68, 1.58)
		normal	12.6		
	$t_{1/2}$ (h)	impaired	35.1 [a]	0.72	(0.45, 1.14)
		normal	49.1 [a]		
RU 42698	AUC_{0-24} (ng•h/mL)	impaired	17591.3	1.35	(0.97, 1.87)
		normal	13067.1		
	C_{max} (ng/mL)	impaired	856.8	1.33	(0.99, 1.80)
		normal	642.4		
	$t_{1/2}$ (h)	impaired	43.0	0.89	(0.61, 1.32)
		normal	48.1 [b]		
RU 42848	AUC_{0-24} (ng•h/mL)	impaired	29210.5	1.06	(0.83, 1.37)
		normal	27447.1		
	C_{max} (ng/mL)	impaired	1405.8	1.12	(0.87, 1.43)
		normal	1258.5		
	$t_{1/2}$ (h)	impaired	39.8	0.79	(0.49, 1.26)
		normal	50.7 [a]		

Mifepristone: Cmax and AUC_{0-24} of mifepristone increased by 30% (CI 0.97, 1.75) and 31 % (CI, 0.99, 1.74), respectively, in subjects with severe renal impairment as compared to healthy subjects. Median Tmax was 1.0 hour for both treatment groups. While half-life was reduced 18% (CI, 0.54-1.25) in subjects with severe renal impairment, it is important to note that samples were taken for a longer period of time in subjects with severe renal impairment; this could have resulted in the identification of another phase to the plasma concentration versus time profile. When plasma protein binding was taken into account,

Reference ID: 3072217

the effect of severely impaired renal function on $C_{max,free}$ was inconclusive as the associated CI (0.67, 1.88) was outside of both the lower and upper bounds of the no-effect boundary. $AUC_{0-24, free}$ increased 19% (CI, 0.81- 1.76) in subjects with severe renal impairment with the upper end of the CI beyond the predefined limit of 1.25.

Metabolites: Cmax increased by 50% (CIs, 1.16-1.95) for RU 42633, 33% (CI, 0.99-1.80) for RU 42698 and 12% (CI, 0.87, 1.43) for RU 42848. AUCO-24 increased by 56% (CI, 1.17- 2.09) for RU 42633, 35% (CI, 0.97-1.87) for RU 42698 and 6% (CI, 0.83-1.37) for RU 42848. For both parameters, the upper ends of the CIs exceeded the predefined boundary of 1.25. There were no statistically significant differences in median T max between the two treatment groups for any of the metabolites. Half-lives were reduced 28% (CI, 0.45-1.14) for RU 42633, 11 % (CI, 0.61-1.32) for RU 42698 and 21 % (CI, 0.49-1.26) for RU 42848. Concentration Comparisons by Time point: Significantly higher total plasma concentrations of mifepristone were observed in subjects with severe renal impairment at 0.5 and 1 hour after dosing on Day 7 (P -0 0.05), and were observed for RU 42633 at 1, 2, 4, 6, 8, 10, 12, 24, 36 and 48 hours after dosing on Day 7 ($P < 0$ 0.05). No effect of severely impaired renal function was observed for plasma concentrations of RU 42698 and RU 42848 at any time point. In addition, no effect of severe renal impairment was observed on the plasma protein unbound concentration of mifepristone or RU 42633 before dosing and at 2 or 8 hours after dosing on Day 7.

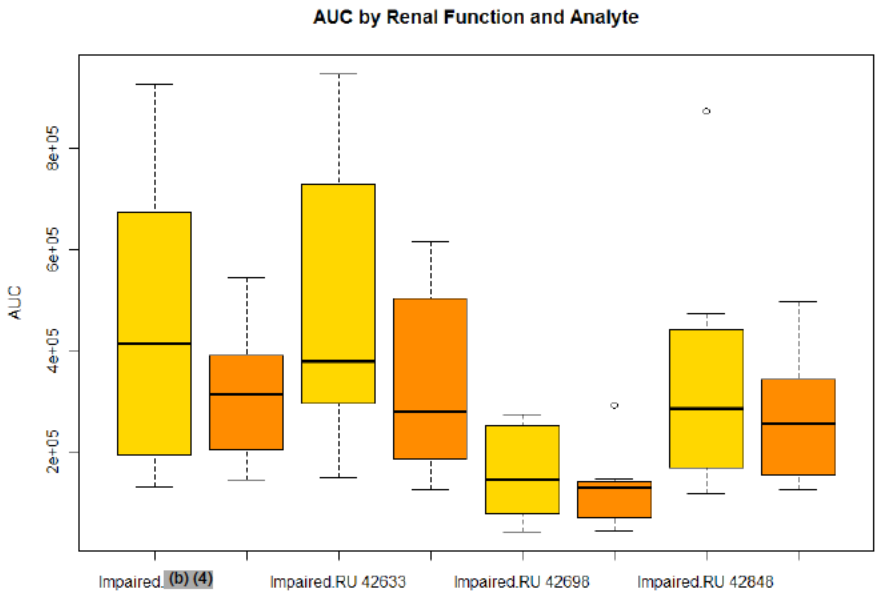
Reviewer's comments and analysis:

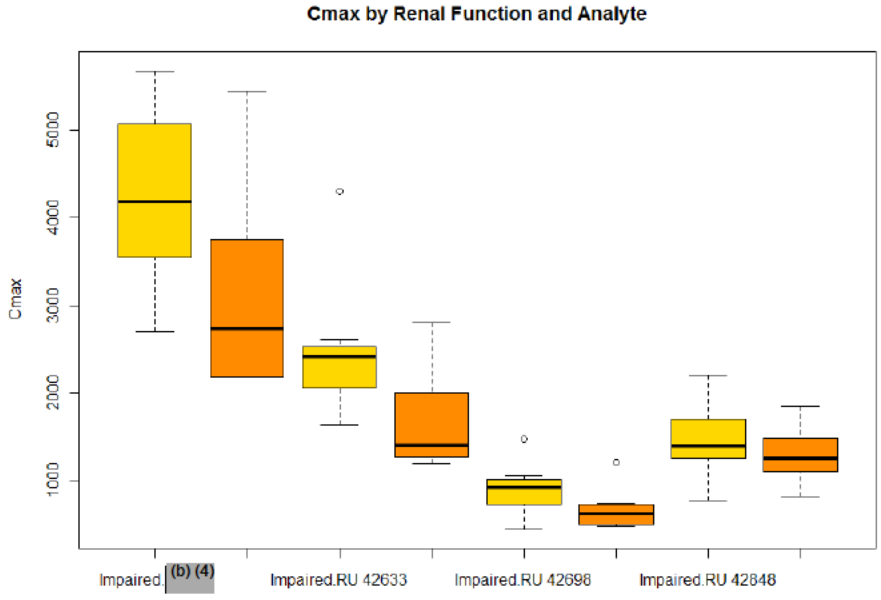
The PK sampling for normal subjects occurred for 14 days (336 hours) while that for subjects with renal impairment occurred for 28 days (672 hours). The statistical comparisons for the exposure of mifepristone and its metabolites were conducted with $AUC_{0-24,}$ and it is less desirable comparison parameters for drugs with nonlinearity than $AUC_{0-336\ hr}$ or $AUC_{0-inf.}$ the reviewer re-conducted the analysis for the comparison of $AUC_{0-inf.}$

Table 17. Statistical analysis for mifepristone and its metabolites (Reviewer's analysis)

Analyte	Parameter	GLSM Ratio	90% CI
Mifepristone	AUC_{0-inf}	1.21	0.71, 2.06
	Cmax	1.30	0.97, 1.75
RU 42633	AUC_{0-inf}	1.43	0.84, 2.44
	Cmax	1.50	1.16, 1.95
RU 42698	AUC_{0-inf}	1.18	0.64, 2.17
	Cmax	1.33	0.99, 1.80
RU 42848	AUC_{0-inf}	1.19	0.71, 1.99
	Cmax	1.12	0.87, 1.43

Reference ID: 3072217


AUC by Renal Function and Analyte
AUC
2e+05
4e+05
6e+05
8e+05
Impaired.
(b) (4)
Impaired.RU 42633
Impaired.RU 42698
Impaired.RU 42848


Cmax by Renal Function and Analyte
Cmax
1000
2000
3000
4000
5000
Impaired.
(b) (4)
Impaired.RU 42633
Impaired.RU 42698
Impaired.RU 42848

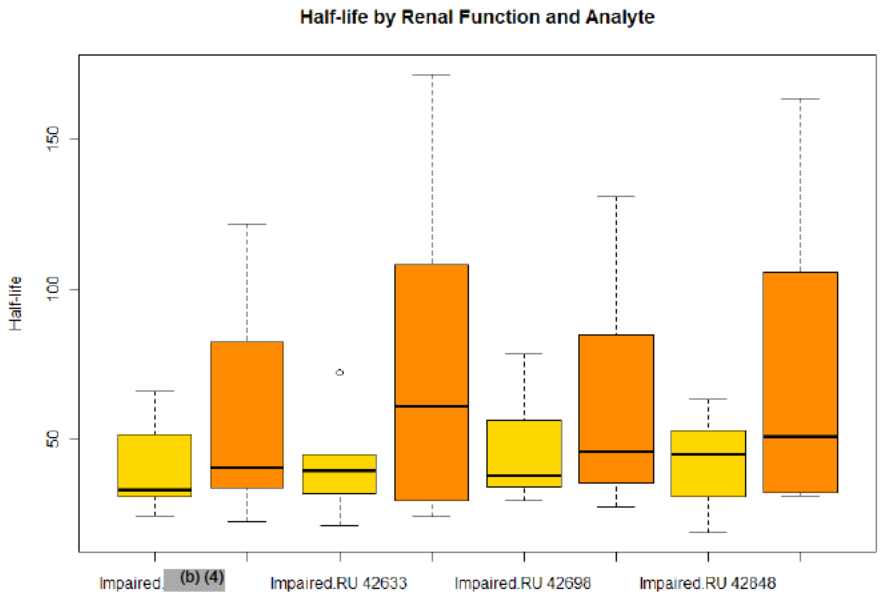


Figure 18. Boxplots for comparison of pharmacokinetics parameters of mifepristone and its metabolites in subjects with normal or with severe renal impairment

The results were quite similar to the sponsor's analysis and no dose adjustment for mifepristone to patients with severe renal impairment was recommended. Furthermore, the dose used in this study was 1200 mg that is the maximum dose, thus the recommendation in the label for the population of renal impairment is acceptable. However, the upper confidence intervals of the geometric least square of mean for each analyte are close to the value 2, and the large interindividual variability renders limited predictability in individual safety. Thus, the administration of mifepristone to patients with renal impairment should be done with caution and the maximum dose should be set to 600 mg as the sponsor proposed.

The half-life decrease in subjects with renal impairment was not anticipated. It is likely due to shorter duration of PK sampling for subjects with severe renal impairment. The pharmacokinetic samples were taken for a longer period in subjects with severe renal impairment.

4.1.3 C-1073-25: DDI with Simvastatin

Title: A Phase 1, Open-Label, Fixed-Sequence, Three-Period Crossover Study to Determine the Effects of Single and Multiple Doses of CORLUX (mifepristone) on the Pharmacokinetics of a Single Dose of Simvastatin in Healthy Volunteers

Objectives	Primary:

Reference ID: 3072217

	• To determine the effects in healthy volunteers of the first and last doses of a multiple dose oral regimen of mifepristone 1200 mg/day on the pharmacokinetics (PK) of single doses of simvastatin, a CYP3A4 substrate with high fist pass metabolic characteristics.
Study Design	Fixed-sequence, 3-treatment, 2-period crossover drug-drug interaction study. Subjects received single doses of simvastatin on 3 occasions: simvastatin 40 mg alone (Day 1), simvastatin 40 mg with a single dose of CORLUX 1200 mg (Day 8), and simvastatin 80 mg with CORLUX 1200 mg on the last day (Day 7) o a 10 day regimen of CORLUX 1200 mg/day (Days 9 ~17). A fixed sequence design was selected from a practical standpoint due to the long terminal half-life of mifepristone (72 hours). Each subject was to serve as his/her own control.
Study population	Twenty subjects were enrolled and 17 subjects (9 males, 8 females) completed the study. Data obtained from 20 subjects were included in the pharmacokinetic analysis. Three subjects were discontinued from the study due to occurrence of AEs.
Treatments	

Treatment	Mifepristone	Simvastatin	Day
TRT A	None	40 mg single dose	1
TRT B	1200 mg/day (first dose)	40 mg single dose	8
TRT C	1200 mg/day (last dose)	80 mg single dose (Day 17)	17

PK Assessment	**Simvastatin**: Serial blood samples were collected on Days 1, 8 and 17 within 30 minutes prior to study drug administration and at 0.5, 1, 1.5,2,3,4,6, 8, 10, 12, and 24 hours postdose. The blood samples (3 ml) were collected Plasma samples were assayed for simvastatin and simvastatin acid using a validated LC-MS/MS method. The limits of detection were 0.05 ng/mL for simvastatin and 0.02 ng/mL for simvastatin acid. Mifepristone/metabolites: Blood samples were collected on Day 8 (pre-dose), Days 16-17 (trough), and Day 18 (24 hours post last dose) to measure plasma concentrations of mifepristone and its metabolites. Plasma samples were assayed for mifepristone and its three active metabolites using a validated LC-MS/MS method. The limits of detection were 10 ng/mL for each analyte.
Safety Assessment	Safety was assessed by physical examinations, vital sign measurements (blood pressure and pulse rate), clinical safety laboratory assessments (clinical chemistry, hematology, urinalysis), and adverse event (AE) monitoring.

Results:

Reference ID: 3072217

Three subjects (Treatment C: simvastatin 80 mg + CORLUX (mifepristone) 1200 mg/day) were discontinued from the study due to the AE, generalized rash.

Pharmacokinetics parameters for simvastatin and simvastatin acid are summarized in Table 18.

Table 18. Mean (±SD) selected pharmacokinetic parameters for simvastatin and simvastatin acid

PK parameter	Simvastatin 40 mg (n = 20) Day 1	Simvastatin 40 mg + Single Dose CORLUX 1200 mg (n = 20) Day 8	Simvastatin 80 mg + Multiple Dose CORLUX 1200 mg/day (n = 17) Day 17
Simvastatin			
C_{max} (ng/mL)	10.2 ± 9.27	26.2 ± 16.2	116 ± 45.7
T_{max} (hours)	1.93 ± 1.56	3.20 ± 2.05	2.65 ± 1.31
AUC_{0-24} (ng-hr/mL)	40.5 ± 20.5	168 ± 87.4	804 ± 278
AUC_{0-inf} (ng-hr/mL)	47.4 ± 23.2	190 ± 97	905 ± 288
Simvastatin Acid			
C_{max} (ng/mL)	1.67 ± 1.14	19.1 ± 15.7	56.5 ± 30.7
T_{max} (hours)	4.85 ± 1.90	5.00 ± 3.25	4.80 ± 2.99
AUC_{0-24} (ng-hr/mL)	16.5 ± 10.6	155 ± 142	493 ± 298
AUC_{0-inf} (ng-hr/mL)	19.2 ± 12.9	164 ± 155	569 ± 349

The first dose of mifepristone multiple dosing increased the exposure of both simvastatin and simvastatin acid drastically. Mean values of Cmax increased from 10.2 ng/mL to 26.2 ng/mL for simvastatin, and from 1.67 ng/mL to 19.1 ng/mL. The mean AUC_{0-inf} increased from 47.4 ng*hr/mL to 190 ng*hr/mL for simvastatin, and from 19.2 ng*hr/mL to 164 ng*hr/mL for simvastatin acid. Simvastatin acid seems to be more sensitive to mifepristone co-administration that simvastatin at early stage of mifepristone multiple dosing. The last dose of mifepristone of 10-day multiple dosing rendered additional increment in exposure of simvastatin and simvastatin acid. Mean values of Cmax increased from 26.2 ng/mL to 116 ng/mL for simvastatin, and from 19.1 ng/mL to 56.5 ng/mL. The mean AUC_{0-inf} increased from 190 ng*hr/mL to 905 ng*hr/mL for simvastatin, and from 164 ng*hr/mL to 569 ng*hr/mL for simvastatin acid.

Pharmacokinetics profiles of simvastatin and simvastatin acid following a single dose of 40 mg simvastatin are depicted in Figure 19.

Reference ID: 3072217

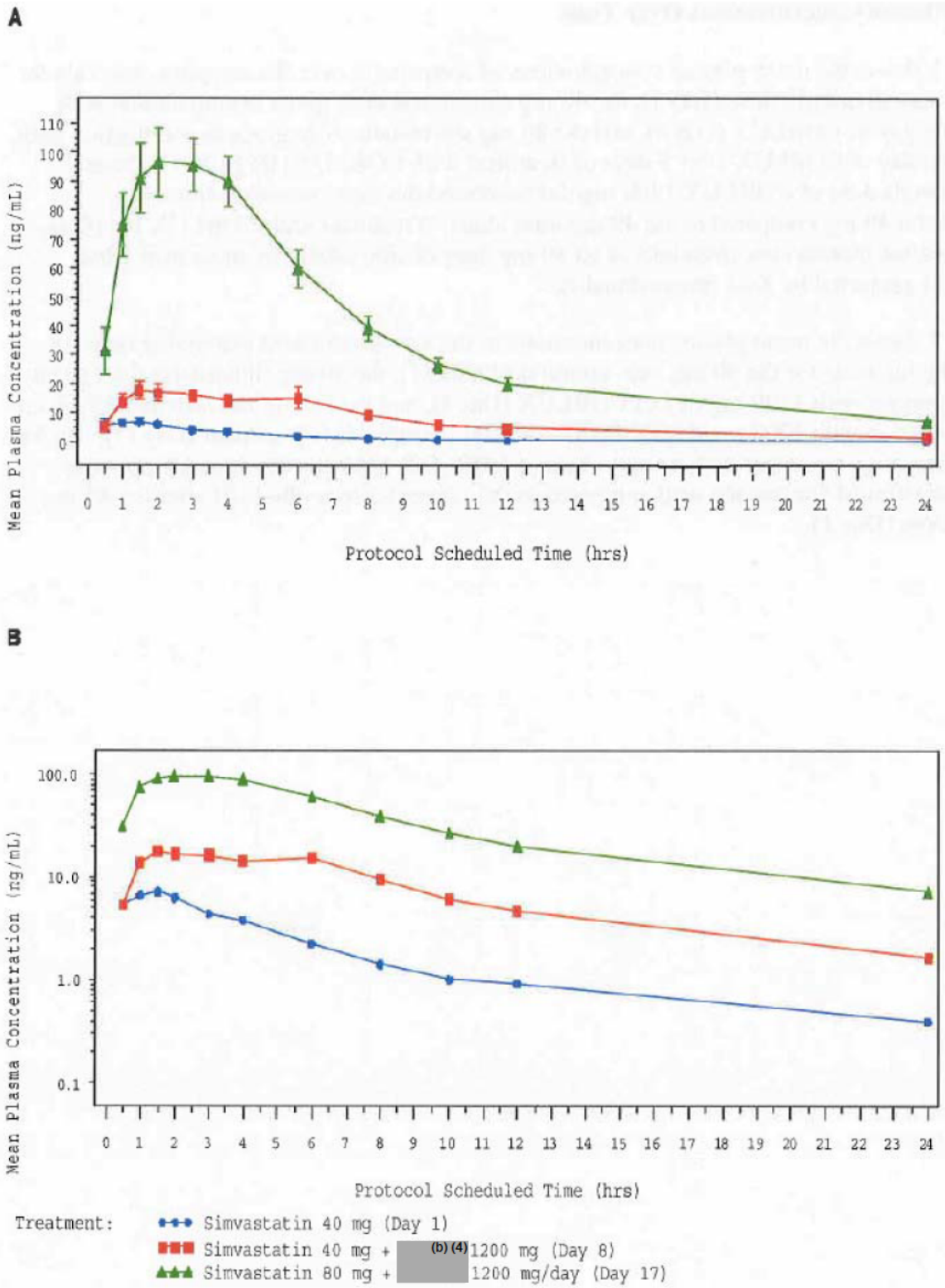


Figure 19. Mean (SD) simvastatin plasma concentrations over time

Table 19. Statistical analysis for pharmacokinetic parameters of simvastatin and simvastatin acid

PK Parameter	Treatment (n)	Geometric Mean	Order	Ratio of Geometric Means	90% CI of Ratio
Simvastatin					
C_{max} (ng/mL)	A: Sim 40 (20)	7.53			
	B: Sim 40+ (b) (4) 20)	22.5	B/A	2.99	2.28-3.92
	C: Sim 80 + (17)	52.8	C/A	7.02	5.27-9.34
			C/B	2.35	1.77-3.13
$AUC_{0\text{-}inf}$ (ng-hr/mL)	A: Sim 40 (20)	41.8			
	B: Sim 40+ (b) (4) 20)	167	B/A	3.99	3.16-5.05
	C: Sim 80 (17)	433	C/A	10.4	8.11-13.21
			C/B	2.59	2.02-3.33
Simvastatin Acid					
C_{max} (ng/mL)	A: Sim 40 (20)	1.37			
	B: Sim 40+ (b) (4) 20)	12.7	B/A	9.21	6.62-12.82
	C: Sim 80 + (17)	25.0	C/A	18.2	12.85-25.79
			C/B	1.98	1.39-2.80
$AUC_{0\text{-}inf}$ (ng-hr/mL)	A: Sim 40 (20)	16.4			
	B: Sim 40+ (b) (4) 20)	109	B/A	6.65	4.91-9.00
	C: Sim 80 + (17)	256	C/A	15.7	11.29-21.70
			C/B	2.35	1.69-3.28

Concomitant administration of a single dose of mifepristone 1200 mg/day resulted in an almost 3-fold increase in Cmax and an almost 4-fold increase in $AUC_{0\text{-}inf}$ for simvastatin. Increases in simvastatin acid Cmax and $AUC_{0\text{-}inf}$, were even greater than 9-fold and almost 7-fold, respectively. The sponsor reported that multiple doses of mifepristone 1200 mg/day for 10 days (Day 17) produced a 7- fold increase in Cmax and a greater than 10- fold increase in $AUC_{0\text{-}inf}$ relative to Day 1. Increases in simvastatin acid Cmax and $AUC_{0\text{-}inf}$ were even greater (greater than 18- fold and almost 16-fold, respectively). Furthermore, the sponsor discussed that these increases resulted in simvastatin and simvastatin acid PK parameter increases of approximately 2- to 3- fold for the last dose of mifepristone as compared to the first dose.

Sixteen subjects reported a total of 32 AEs. Twelve subjects in Treatment period C (Simvastatin 80 mg + CORLUX 1200 mg/day) reported a total of 21 AEs, 5 subjects in Treatment period B (Simvastatin 40 mg + CORLUX 1200 mg) reported 6 AEs, and 4 subjects in Treatment period A (Simvastatin 40 mg) reported 4 AEs. Of the 32 treatment-emergent AEs, 26 were mild and six were of moderate intensity. There were 14 treatment-related AEs with 8 mild and 6 of moderate intensity. The most commonly reported AEs were headache, generalized rash, dry mouth, and constipation. All the AEs were resolved. There was no life- threatening or fatal AE reported in the study.

Conclusion and reviewer's comments: The surprisingly significant drug-drug interaction between mifepristone and simvastatin was presented in this study. Although the increase in exposure of CYP3A4 substrates were anticipated, the magnitudes were greater than anticipated. Use of simvastatin should be contraindicated with concomitant administration of mifepristone. One thing should be noted that the magnitude of drug-interaction for the effect of multiple doses of mifepristone on the pharmacokinetics of simvastatin and its acid metabolite is exaggerated due to the confounder given by inadequate study design. The dose of simvastatin for Treatment C is 80 mg while the dose for other treatments is 40 mg. Thus, the statistically comparisons between

Reference ID: 3072217

Treatments A and C and Treatments B and C should be understood with the consideration of dose differences.

4.1.4 C-1073-23: DDI with Digoxin

Title: A Phase 1, Open-Label, Fixed-Sequence, Three-Treatment Study to Determine the Effect of Single and Multiple Doses of Mifepristone on the Pharmacokinetics of Digoxin at Steady State

<table>
<tr><td>Objectives</td><td>Primary:
• To determine the effect of the first and last oral doses of a multiple dose regimen of mifepristone 1200 mg/day on the pharmacokinetics of digoxin at steady state</td></tr>
<tr><td>Study Design</td><td>Open-label, fixed-sequence, three-treatment drug-drug interaction study. Subjects received digoxin alone for 7 days followed by digoxin in combination with mifepristone for 10 days. Steady state profiles of digoxin plasma and urine concentrations were obtained under three conditions: alone (Day 7), on the first day of dosing of mifepristone 1200 mg (Day 8) and on the last day of ten-day regimen of mifepristone 1200 mg/day (Day 17). For safety reasons, trough concentrations of digoxin were determined locally (24-hour turnaround time) every 1 to 2 days during dosing. Subjects who achieved an alert concentration were to be terminated early from the study. Two-hour urine collections along with a single blood sample were obtained periodically during mifepristone and digoxin dosing to determine digoxin renal clearance. In addition, blood samples for determination of pre-dose concentrations of mifepristone and its metabolites were taken periodically during mifepristone dosing. Subjects were confined from the evening of Day 0 until the morning of Day 18. A final safety evaluate was performed 3 weeks after the last dose of mifepristone.</td></tr>
<tr><td>Study population</td><td>Twenty four (14 males, 10 females) enrolled and 20 subjects completed the study. Pharmacokinetics analysis was performed with data obtained from 22 subjects.</td></tr>
<tr><td>Treatments</td><td>
<table>
<tr><th>Treatment</th><th>Day</th><th>Digoxin</th><th>Mifepristone</th><th>N</th></tr>
<tr><td>A</td><td>1
2-7</td><td>0.25 mg every 6 hours × 3 doses
0.125 mg/day</td><td>-</td><td>22</td></tr>
<tr><td>B</td><td>8</td><td>0.125 mg × 1 dose</td><td>1200 mg/day (first dose_</td><td>22</td></tr>
<tr><td>C</td><td>9-17</td><td>0.125 mg/day</td><td>1200 mg/day (last dose)</td><td>22</td></tr>
</table>
</td></tr>
<tr><td>Investigational drugs</td><td>Corlux 300 mg tablet (lot 9J03)
Lanoxin (digoxin) 0.125 mg tablet (lot A38307)</td></tr>
<tr><td>PK</td><td>Digoxin: Serial blood sampling was performed on Days 7, 8 and 17</td></tr>
</table>

Reference ID: 3072217

Assessment	within 30 minutes prior to digoxin administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 15, and 24 hours post dose. On Days 7, 8 and 17, interval urine collections were obtained at 0 ~12 hours and 12 ~24 hours post dose. On Days 10, 12 and 14, 2-hour urine collections were obtained and a blood sample was taken midway through the urine collection. Plasma and urine samples were assayed for digoxin using LC/MS/MS methods by [redacted] (b) (4). The limit of detection of the plasma assay was 0.1 ng/mL, while the limit of the urine assay was 0.5 ng/mL. Trough plasma concentrations were determined locally (24 hour turnaround time) on Days 2, 4, 6 ~10, 12, 14 and 16. Digoxin pharmacokinetic parameters calculated from plasma and urine concentrations included Tmax, Cmax and AUC_{0-24}, amount excreted (Ae), % excreted and renal clearance (CLr). Log-transformed PK parameters for AUC_{0-24}, Cmax, Ae%, and CLr, were analyzed using a mixed-effects model with day as a fixed effect and subject as a random effect. The 90% confidence interval (CI) of the ratio of the geometric means of the PK parameters for Day 8 (first mifepristone dose) and Day 17 (last mifepristone dose) were compared with Day 7 (digoxin alone). Less than a 30% increase or decrease in the parameter was determined if the 90% CIs were contained within the interval 0.70 to 1.43. **Mifepristone:** Pre-dose and trough total plasma concentrations of mifepristone and its metabolites were determined on Days 8, 9, 15, 16 and 17. [redacted] (b) (4) assayed all plasma samples for mifepristone and the 3 active metabolites (RU 42633, RU 42698 and RU 42848) using a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) assay. The lower limit of detection of this method was 10 ng/mL for each analyte.
Safety Assessment	Safety assessments included monitoring of adverse events (AEs), clinical laboratory tests (including local laboratory monitoring of digoxin trough plasma concentrations on Days 2, 4, 6 through 10, 12, 14, and 16), vital sign measurements, physical examinations, and 12-lead electrocardiograms (ECGs).

Results:

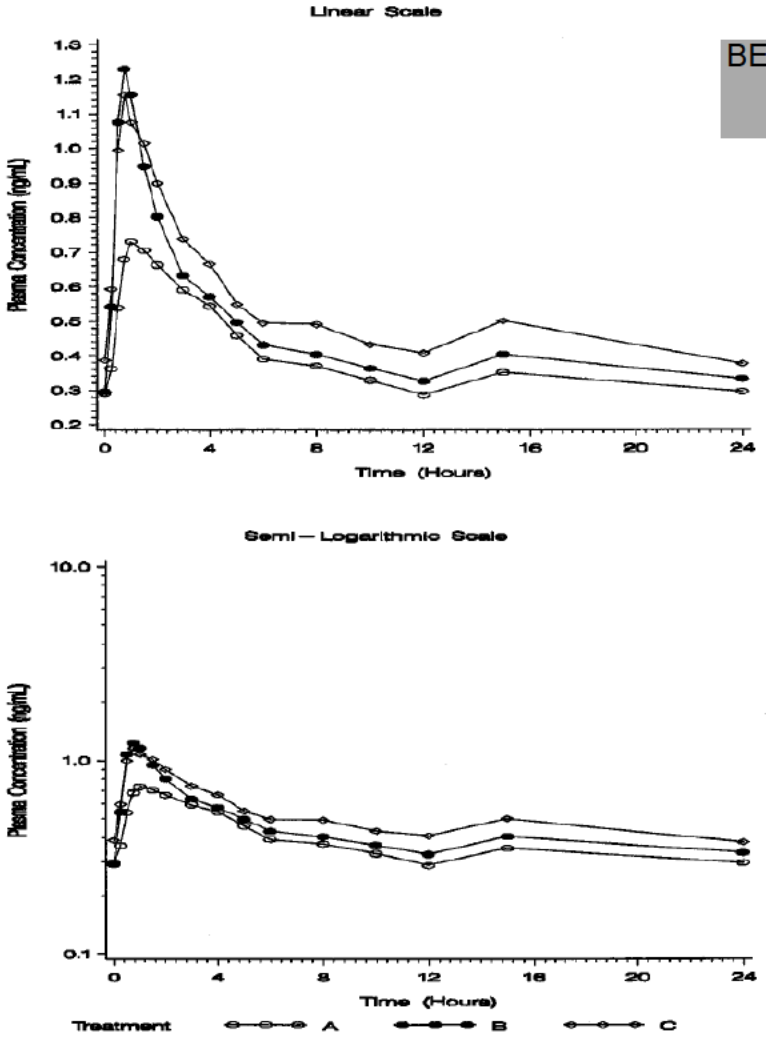
Due to the half-life of digoxin (approximately 1.6 days), the sponsor designed the study under steady-state condition of digoxin. To achieve steady state quickly, three doses of 0.25 mg digoxin was administered with 6-hour interval on Day 1. These feature of the study design should be remembered when the study results are interpreted. Descriptive statistics for the digoxin pharmacokinetic parameters are provided in Table 20.

Table 20. Statistical summary of digoxin following Treatments A, B, and C.

Reference ID: 3072217

Parameter	Treatment Mean (CV)		
	Digoxin 0.125 mg/day Multiple Dose (N = 22)	Digoxin 0.125 mg/day (Multiple Dose) + MIFE 1200 mg/day (First Dose) (N = 22)	Digoxin 0.125 mg/day (Last Dose) + MIFE 1200 mg/day (Last Dose) (N = 22)
AUC_{0-24} (ng•h/mL)	9.27 (29)	10.85 (24)	12.57 (19)
C_{max} (ng/mL)	0.78 (30)	1.30 (26)	1.26 (26)
T_{max} (h)[a]	1.00 (0.50, 3.00)	0.75 (0.50, 3.00)	0.75 (0.50, 2.00)
CL_r (L/h)	6.91 (17)	6.64 (19)	6.11 (19)
Ae%	50 (25)	56 (24)	60 (17)

MIFE: mifepristone, CV: coefficient of variation.
Source: Clinical Study Report (Table 14.2.3)



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TRT A: digoxin 0.125 mg/day (multiple doses) +0.75 mg loading dose
TRT B: digoxin 0.125 mg (multiple doses) + mifepristone 1200 mg (first dose)
TRT C: digoxin 0.125 mg (multiple doses) + mifepristone 1200 mg (last dose)

Figure 20. Mean concentrations versus time profiles of digoxin by Treatment

The statistical analysis results are shown in Table below.

Reference ID: 3072217

Table 21. Statistical comparison of Treatments A, B, and C

Parameter	Treatment[a]	N	Geometric Mean	Treatment Comparison	Ratio of Geometric Means	90% CI
AUC_{0-24} (ng•h/mL)	A	22	8.82	**B/A**	**1.19**	**1.13–1.25**
	B	22	10.51	C/A	1.40	1.33–1.47
	C	22	12.34	**C/B**	**1.17**	**1.12–1.24**
C_{max} (ng/mL)	A	22	0.74	B/A	1.68	1.54–1.84
	B	22	1.25	C/A	1.64	1.50–1.79
	C	22	1.22	**C/B**	**0.97**	**0.89–1.07**
CL_r (L/h)	A	22	6.81	**B/A**	**0.96**	**0.91–1.00**
	B	22	6.52	**C/A**	**0.88**	**0.84–0.92**
	C	22	6.01	**C/B**	**0.92**	**0.88–0.96**
Ae%	A	22	48.04	**B/A**	**1.14**	**1.06–1.22**
	B	22	54.83	**C/A**	**1.23**	**1.15–1.32**
	C	22	59.31	**C/B**	**1.08**	**1.01–1.16**
T_{max}[b]	A	22	1.00 (0.50, 3.00)	B/A	NA	NA
	B	22	0.75 (0.50, 3.00)	C/A	NA	NA
	C	22	0.75 (0.50, 2.00)	C/B	NA	NA

Treatment A: digoxin 0.125 mg/day + 0.75 mg loading dose
Treatment B: digoxin 0.125 mg/day + mifepristone 1200 mg/day (first dose)
Treatment C: digoxin 0.125 mg/day (last dose) + mifepristone 1200 mg/day (last dose)
Bold indicates CI within predefined boundary of 0.70 to 1.43.

Cmax values of digoxin were increased when digoxin was administered with the first dose (ratio, 1.68, CI, 1.54-1.84) and the last dose of mifepristone (ratio, 1.64, CI, 1.50-1.79) with the lower and upper end of the CIs exceeding the upper predefined boundary of 1.43. Digoxin AUC_{0-24hr} was higher after the last dose of mifepristone as compared to when it was administered alone (ratio 1.40, CI, 1.33-1.47) with the upper bound of the CI exceeding the predefined limit of 1.43. However AUC_{0-24} was deemed equivalent (i.e., less than a 30% change) when digoxin was administered with the first dose of mifepristone compared to alone (ratio 1.19, CI 1.13-1.25). The CLr and Ae% values for digoxin were equivalent in the presence of either the first or last of the multiple doses of mifepristone. Tmax median estimates and their ranges were similar for all three treatment groups. Digoxin PK parameters were equivalent when digoxin was administered with the last dose of mifepristone compared to administration with the first dose of mifepristone.

Reviewer's comments: The reference treatment (Treatment A, 0.125 mg of digoxin) was administered with significant amount of loading dose (0.75 mg of digoxin) to achieve steady state faster. The effect of mifepristone on the pharmacokinetics of digoxin was assessed under steady-state condition of digoxin with maintenance dose of 0.125 mg. However, the reference treatment on Day 7 could be still under the influence of significant amount of loading dose, which was given on Day 1 to achieve steady state faster. The half-life of digoxin is about 1.6 days as the sponsor reported. Theoretically, the steady state can be achieved by the end of Day 8. Thus, the comparisons of digoxin PK on Day 7 without concomitant administration of mifepristone to digoxin PK on Day 8 with concomitant administration of mifepristone would not be desirable in predicting the true effect of mifepristone on digoxin. Digoxin exposure on Day 7 would be greater than

Reference ID: 3072217

that on Day 8 without co-administration of mifepristone since the loading dose may be still being cleared along with the maintenance doses. This theoretical concern was partially resolved at least for the steady-state assumption for Day 7 and Day 8 by checking the pre-dose concentrations on Day 7 and Day 8 (Figure 21). Although, the evidence is insufficient to declare drug-drug interaction with digoxin, clinical monitoring along with measurements of digoxin concentrations after 1~2 weeks of concomitant use is recommended as the sponsor indicates in the labeling.

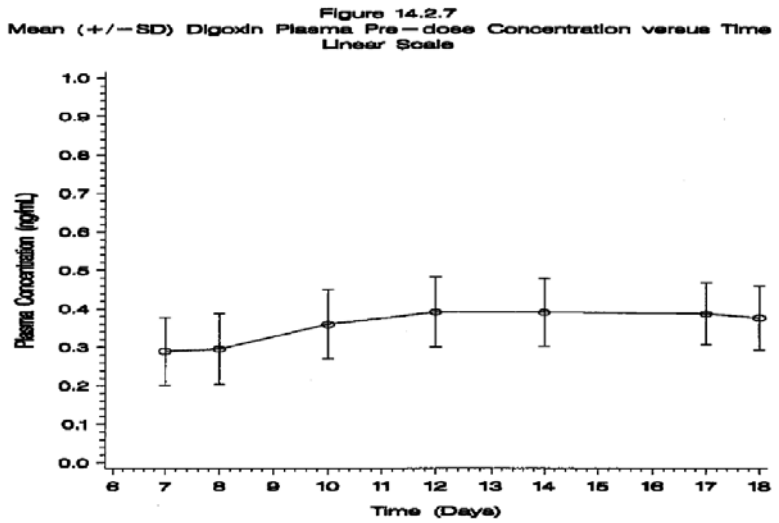

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Figure 21. Pre-dose concentrations of digoxin

The sponsor reported that Cmax values of digoxin were increased when digoxin was administered with the first dose (ratio, 1.68, CI, 1.54-1.84) and the last dose of mifepristone (ratio, 1.64, CI, 1.50-1.79). Digoxin $AUC_{0\text{-}24hr}$ was higher after the last dose of mifepristone as compared to when it was administered alone (ratio 1.40, CI, 1.33-1.47) with loading doses. The sponsor even claimed that $AUC_{0\text{-}24}$ was deemed equivalent when digoxin was administered with the first dose of mifepristone compared to alone (ratio 1.19, CI 1.13-1.25). However, 64% increase in Cmax and 40% increase in AUC are considered significant interaction for digoxin that has a narrow therapeutic widow. According to the labeling of digoxin, before concomitant use of drugs which indicated interaction to similar extent (e.g., digoxin's Cmax and AUC were increased 58% and 39%, respectively by captopril, and 57% and 15%, respectively by nitrendipin), serum concentrations of digoxin should be measured. Then digoxin dose should be reduced by approximately 30% to 50% and monitored continuously. Therefore, the same dosing recommendations are applied to digoxin.

4.1.5 C-1073-24: DDI with Alprazolam

Title: A Phase 1, Open-Label, Fixed-Sequence, Three-Period Crossover Study to Determine the Effect of Single dose and Multiple Doses of Mifepristone on the Pharmacokinetics of a Single Dose of Alprazolam in Healthy Volunteers

Reference ID: 3072217

Objectives	Primary: • To determine the effect in healthy volunteers of single and multiple oral doses of mifepristone on the pharmacokinetics of single doses of alprazolam, a prototypical CYP3A4 substrate with low first-pass effect. Secondary: • To determined the effect of gender on alprazolam PK
Study Design	Open-label, fixed-sequence, 3-period, crossover drug-drug interaction study. Subjects received a single 1-mg dose of alprazolam on 3 occasions: alone on Day 1 (Treatment A), with a single 1200-mg dose of mifepristone on Day 8 (Treatment B), and at the time of the tenth dose of mifepristone 1200 mg/day on Day 20 during a 12-course (Treatment C). There was a 7-day washout between the first 2 doses and a 12-day washout between the last 2 doses of alprazolam. Serial 72-hour blood samples for determination of plasma concentrations of alprazolam and 4-hydroxyalprazolam were obtained after each dose of alprazolam. Blood samples for determination of pre-dose and trough plasma concentrations of mifepristone and its metabolites were obtained periodically. PD assessment for different indication was also performed but irrelevant to this submission.
Study population	Sixteen subjects enrolled (8 males/8 females); all completed the study resulting in a PK population of 16 subjects. Mean age was 47.6 years (range, 26-63).
Treatments	

	Mifepristone	Alprazolam	Day
TRT A	None	1 mg single dose	1
TRT B	1200 mg single dose	1 mg single dose	8
TRT C	1200 mg/day multiple dose	1 mg single dose	20

PK Assessment	**Alprazolam:** Pharmacokinetics - Serial blood sampling for plasma concentrations of alprazolam and its metabolite (4-hydroxyalprazolam) was performed within 30 minutes prior to dosing on Days 1, 8, and 20 and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15, 24, 36, 48, 60, and 72 hours after dosing. Plasma samples were assayed for alprazolam and 4-hydroxyalprazolam using a validated LCIMSIMS method by (b) (4) [redacted]. The limits of detection are 0.025 ng/mL for both alprazolam and 4-hydroxyalprazolam PK parameters calculated for alprazolam and 4-hydroxyalprazolam included Cmax, Tmax, AUC_{0-t}, AUC_{0-72hr}, AUC_{0-inf}, AUC_{0-inf} extrapolated, Ke, and $T_{1/2}$. Log-transformed PK parameters were analyzed and 90% confidence intervals (CIs) were calculated on the geometric least squares means using a mixed-effect analysis of variance (ANOVA) model with treatment as a fixed effect and subject as a random effect. Less than a 20% increase or decrease in AUC was determined if the 90% CIs were contained within

	the interval of 0.8 to 1.25. The effect of gender on the pharmacokinetics of alprazolam was explored by repeating the mixed-effect ANOVA model with treatment, gender, and treatment-by-gender as fixed effects and subject as a random effect. **Mifepristone:** Blood sampling for plasma concentrations of mifepristone and its 3 active metabolites (RU 42633, RU 42698, and RU 42848) was performed within 30 minutes before dosing on Day 8, 19, and 20 as well as 24 hours after the last dose on Day 21. (b) (4) assayed all plasma samples for mifepristone and the 3 active metabolites (RU 42633, RU 42698 and RU 42848) using a validated LC/MS/MS assay. The lower limit of detection of this method was 10 ng/mL for each analyte.
PD Assessment	Conducted but not its endpoints were not relevant to the current submission. See reviewer's comments.

Results:

PD: The sponsor performed and reported PD assessment for PD endpoints of sedation and mood. This study seems to have been conducted when the sponsor was investigating this compound for another indication. Since these endpoints are not relevant to this submission, PD assessments have not been reviewed.

PK:

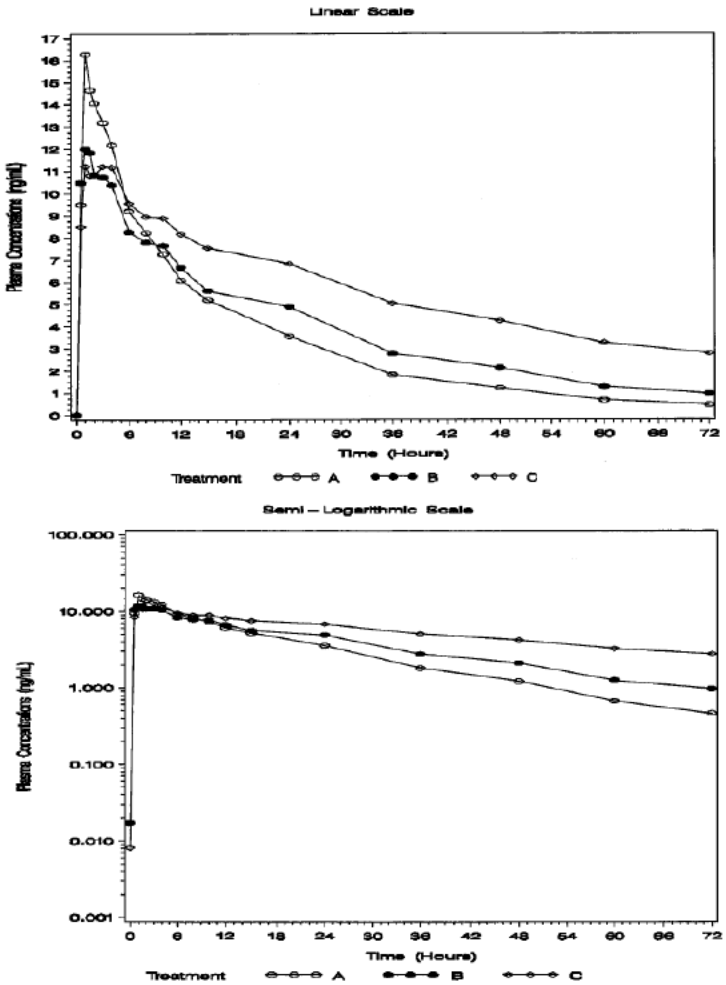
Pharmacokinetic parameters for alprazolam and 4-hydroxyalprazolam are summarized in Table below.

Table 22. Summary of pharmacokinetic parameters of alprazolam and 4-OH alprazolam

Parameter	Treatment Mean (CV)		
	Treatment A Single 1-mg Alprazolam Dose (N = 16)	Treatment B Single 1-mg Alprazolam Dose + Single 1200-mg Mifepristone Dose (N = 16)	Treatment C Mifepristone 1200-mg/day (Multiple Dose) + Single 1-mg Alprazolam Dose (N = 16)
Alprazolam			
AUC_{0-t} (ng•h/mL)	242.9 (40)	280.7 (29)	411.2 (21)
AUC_{0-inf} (ng•h/mL)	255.7 (45)	312.6 (34)	360.9 (12)[a]
C_{max} (ng/mL)	17.3 (38)	14.9 (36)	13.1 (20)
T_{max} (h)[b]	1.00 (0.50, 4.00)	1.00 (0.50, 4.00)	1.25 (0.50, 6.00)
$t_{1/2}$ (h)	14.9 (28)	20.3 (21)	37.6 (28)[c]
4-Hydroxyalprazolam			
AUC_{0-t} (ng•h/mL)	28.1 (44)	33.3 (34)	20.1 (36)
AUC_{0-inf} (ng•h/mL)	29.2 (42)	35.3 (33)	28.4 (39)[a]
C_{max} (ng/mL)	1.22 (40)	1.48 (42)	0.46 (42)
T_{max} (h)[b]	2.50 (1.00, 12.00)	2.00 (1.00, 8.00)	12.00 (1.50, 15.00)
$t_{1/2}$ (h)	14.7 (25)	17.9 (20)	32.8 (23)[d]

Reference ID: 3072217

[a] n=5. Values of $AUC_{0\text{-}inf}$ were excluded from the summary statistics and statistical analyses if the extrapolated fraction of $AUC_{0\text{-}inf}$ was greater than 20%
[b] Median (minimum, maximum) values are presented
[c] n=15
[d] n=14



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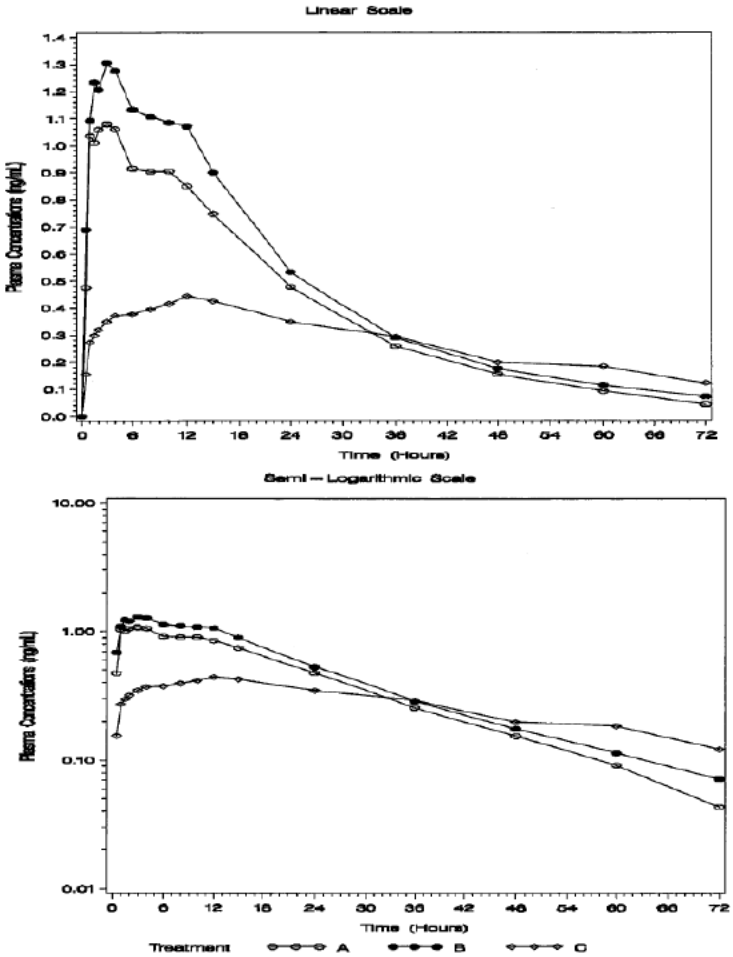
Treatment A = single 1-mg alprazolam dose alone (Day 1).
Treatment B = single 1-mg alprazolam dose and a single 1200-mg (b) (4) dose (Day 8).
Treatment C = daily 1200-mg (b) (4) doses (Days 11 to 22) with a single 1-mg alprazolam dose (Day 20).

Figure 22. Mean p a concentration of alprazolam versus time profile by treatment



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Treatment A = single 1-mg alprazolam dose alone (Day 1).
Treatment B = single 1-mg alprazolam dose and a single 1200-mg (b) (4) dose (Day 8).
Treatment C = daily 1200-mg (b) (4) doses (Days 11 to 22) with a single 1-mg alprazolam dose (Day 20).

Figure 23. Mean plasma concentration of 4-hydroxyalprazolam versus time profile by treatment

The sponsor's report of the statistical analysis for the effects of mifepristone on the PK of alprazolam and 4-OH alprazolam are described in Table 23.

Table 23. Statistical Analysis of Mifepristone Effect on the Plasma Pharmacokinetic Parameters of Alprazolam and 4-Hydroxyalprazolam (Source: Clinical Study Report (Tables 14.2.3.1 and 14.2.3.3)

Analyte	Parameter	Treatment	N	GM	Test/Reference	Ratio of GLSM	90%CI
Alprazolam	AUC_{0-t} (ng*h/mL)	A	16	223.29	-	-	-
		B	16	269.79	B/A	1.21	1.02-1.44
		C	16	402.85	C/A	**1.80**	**1.52-2.15**
					C/B	1.49	1.26-1.78
	AUC_{0-inf} (ng*h/mL)	A	16	232.65	-	-	-
		B	16	296.35	B/A	1.27	1.04-1.57
		C	4[a]	389.24	C/A	**1.67**	**1.18-2.37**
					C/B	1.31	0.93-1.86
	Cmax (ng/mL)	A	16	15.80	-	-	-
		B	16	14.14	B/A	0.89	0.74-1.08
		C	16	12.87	C/A	**0.81**	**0.67-0.99**

Reference ID: 3072217

					C/B	0.91	0.75-1.10
4-OH Alprazolam	AUC_{0-t} (ng*h/mL)	A	16	24.99	-	-	-
		B	16	31.60	B/A	1.26	1.07-1.49
		C	16	18.92	C/A	**0.76**	**0.64-0.89**
					C/B	0.60	0.51-0.71
	AUC_{0-inf} (ng*h/mL)	A	16	26.20	-	-	-
		B	16	33.53	B/A	1.28	1.07-1.54
		C	5[a]	24.55	C/A	**0.94**	**0.70-1.25**
					C/B	0.73	0.55-0.98
	Cmax (ng/mL)	A	16	1.09	-	-	-
		B	16	1.37	B/A	1.25	1.03-1.52
		C	16	0.42	C/A	**0.39**	0.32-0.47
					C/B	0.31	0.25-0.38

[a] AUC_{o-inf} results were excluded from summary statistics and statistical analysis for subjects whose extrapolated fraction of AUC_{0-inf} was greater than 20%.

AUC_{0-t} of alprazolam and 4-OH alprazolam following 1 mg of alprazolam increased 80% (n=16) and 76% (n=16) , respectively with concomitant administration of multiple doses of 1200 mg/day mifepristone for 10 days compared to those following 1 mg of alprazolam alone. AUC_{0-inf} of alprazolam and 4-OH alprazolam following 1 mg of alprazolam increased 67% (n=4) and 94% (n=5), respectively with concomitant administration of multiple doses of 1200 mg/day mifepristone for 10 days compared to those following 1 mg of alprazolam alone. Cmax of alprazolam and 4-OH alprazolam following 1 mg of alprazolam decreased by 19% (n=16) and 61% (n=16), respectively with concomitant administration of multiple doses of 1200 mg/day mifepristone for 10 days compared to those following 1 mg of alprazolam alone. The half-life increase in both alprazolam and 4-OH alprazolam can increase of AUC while Cmax is decreasing with co-administration of mifepristone.

Reviewer's analysis and comments:

The sponsor's conclusion over the drug-drug interaction was acceptable, although the reviewer had to reassure since the magnitude of the drug-drug interaction was smaller than the magnitude obtained from the drug-drug interaction study with another CYP3A4 substrate, simvastatin. Furthermore, the sponsor used AUC_{0-inf} for the exposure comparison but the number of subjects used in AUC_{0-inf} comparison was only four after dropping subjects with extrapolated portion of AUC_{0-inf} greater than 20%. If it is the case, the AUC_{0-t} instead of AUC_{0-inf} can be in the drug-drug interaction, and the sponsor in fact used AUC_{0-t} as the main measurement of exposure. However, it is still needed to assess AUC_{0-inf} from all subjects as reference because of the fact that half-life of alprazolam seems to increase with co-administration of mifepristone. The concentrations of 4-hyrdoxyaplrazolam profiles clearly indicate that mifepristone significantly inhibit the metabolism of alprazolam.

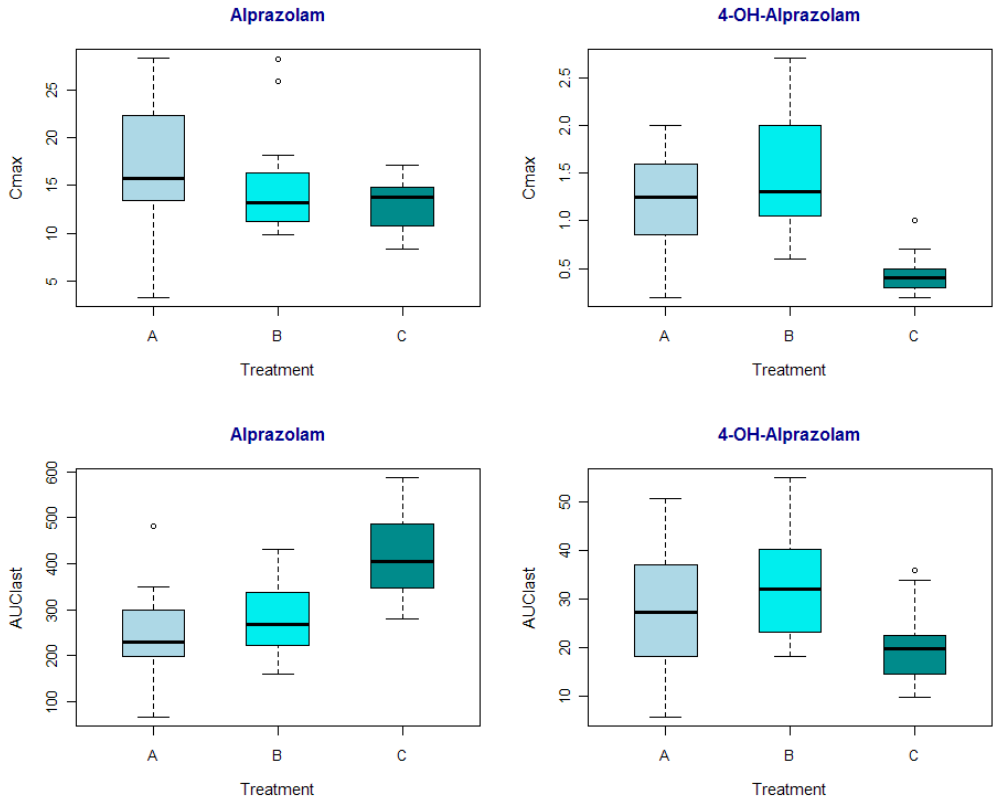
Reviewer's analysis resulted in small difference in the ratio of geometric mean ratio of Cmax and AUC for both alprazolam and 4-Hydroxyalprazolam as shown in Table 24.

Table 24. Reviewer's Analysis Results for the Effect of Mifepristone on Alprazolam PK [a]

Reference ID: 3072217

Parameter	Analyte	Test/Reference	Ratio of GLSM	CI_90_Lower	CI_90_Upper
$AUC_{0\text{-}inf}$	4-OH-Alprazolam	B/A	1.276	1.083	1.503
	4-OH-Alprazolam	C/A	0.953	0.809	1.123
	Alprazolam	B/A	1.272	1.053	1.538
	Alprazolam	C/A	**2.366**	**1.958**	**2.86**
$AUC_{0\text{-}t}$	4-OH-Alprazolam	B/A	1.265	1.071	1.494
	4-OH-Alprazolam	C/A	**0.758**	**0.641**	**0.895**
	Alprazolam	B/A	1.208	1.015	1.438
	Alprazolam	C/A	**1.805**	**1.516**	**2.148**
Cmax	4-OH-Alprazolam	B/A	1.25	1.025	1.524
	4-OH-Alprazolam	C/A	0.388	0.318	0.473
	Alprazolam	B/A	0.895	0.739	1.084
	Alprazolam	C/A	0.814	0.672	0.986

[a] The comparison between the first dose of mifepristone and the last dose of mifepristone on alprazolam PK was omitted due to its low relevance.



The results obtained from the reviewer's analysis do not show large difference from those of the sponsor's analysis, except the $AUC_{0\text{-}inf}$ from all subjects can be compared with $AUC_{0\text{-}t}$. The $AUC_{0\text{-}inf}$ from all subjects increased by 2.4 fold. Thus, it would be reasonable to expect 2-fold increase in alprazolam exposure with concomitant administration of mifepristone.

Reference ID: 3072217

4.1.6 C-1073-26: DDI with Cimetidine

Title: A Phase 1, Open-Label, Fixed-Sequence, Two-Period, Three-Treatment Crossover Study to Determine the Effects of Multiple Doses of Cimetidine on the Pharmacokinetics of CORLUX (mifepristone) in Healthy Volunteers

<table>
<tr><td>Objectives</td><td>Primary:
• To determine the effects of single and multiple oral doses of cimetidine on the pharmacokinetics of single dose and multiple oral doses of CORLUX
• To determine the effects of single and multiple oral doses of CORLUX on the urinary excretion of unchanged cimetidine in healthy volunteers</td></tr>
<tr><td>Study Design</td><td>Open-label, fixed-sequence, 3-period, 6-treatment crossover drug-drug interaction study</td></tr>
<tr><td>Study population</td><td>Twenty subjects were enrolled, and included in the PK and safety analyses</td></tr>
<tr><td>Investigational drug</td><td><table><tr><th>Drug</th><th>Potency</th><th>Dosage Form</th></tr><tr><td>CORLUX</td><td>300 mg</td><td>Tablet</td></tr><tr><td>Cimetidine</td><td>800 mg</td><td>Tablet</td></tr></table></td></tr>
<tr><td>Treatments</td><td><table><tr><th>Period</th><th>Treatment</th><th>Cimetidine</th><th>CORLUX</th></tr><tr><td>1</td><td>TRT A</td><td>800 mg SD</td><td></td></tr><tr><td>2</td><td>TRT B</td><td></td><td>300 mg SD</td></tr><tr><td>3</td><td>TRT C</td><td>800 mg SD</td><td>300 mg MD (1st day)</td></tr><tr><td>3</td><td>TRT D</td><td></td><td>300 mg MD (7th day)</td></tr><tr><td>3</td><td>TRT E</td><td>800 mg MD (1st day)</td><td>300 mg MD (8th day)</td></tr><tr><td>3</td><td>TRT F</td><td>800 mg MD (8th day)</td><td>300 mg MD (14th day)</td></tr></table></td></tr>
<tr><td>Reference Treatment</td><td>TRT A: single 800-mg cimetidine tablet administered orally on Day 1 of Period 1
TRT B: single 300-mg CORLUX tablet administered orally on Day 1 of Period 2</td></tr>
<tr><td>PK Assessment</td><td>Mifepristone: Two serial profiles)one 14-day and one 28-day) of plasma concentrations of mifepristone and its metabolites were obtained to determine the terminal elimination half-life in the presence and absence of single and multiple doses of cimetidine (Day 1 of Period 2 [14-day] and Day 14 of Period 3 [28-day]). Three 24-hour profiles of plasma concentrations of mifepristone and its metabolites were also determined in Period 3 on Day 1 (first dose of CORLUX in combination with a single dose of cimetidine, on Day 7 (multiple doses of CORLUX alone), and on Day 8 (multiple doses of CORLUX in combination with the first dose of cimetidine). In addition, trough blood samples were obtained on Days 5, 6, and 10 through 13 of Period 3. The following PK parameters were calculated from plasma concentrations of mifepristone and its metabolites: area under the plasma concentration-time curve</td></tr>
</table>

Reference ID: 3072217

	from time 0 to the last quantifiable concentration after dosing (AUC_{0-last}); area under the plasma concentration curve from time 0 to 24 hours after dosing (AUC_{0-24}), area under the plasma concentration-time curve from time 0 to 72 hours after dosing (AUC_{0-72}), area under the plasma concentration-time curve from time 0 to extrapolated infinity (AUC_{0-inf}), maximum observed plasma concentration (Cmax), time to maximum observed plasma concentration (Tmax), and t1/2. **Cimetidine (Plasma):** From the second aliquot of plasma samples that were collected as backup for determination of concentrations of mifepristone and its metabolites, plasma concentrations of cimetidine on Days 1, 8, and 14 of Period 3 (Treatments C,D, E, and F) were used to calculate the following PK parameters: AUC_{0-last}, AUC_{0-24}, $AUC_{0-inf,}$ Cmax, Tmax, t1/2. **Cimetidine (Urine):** Four 24-hour urine collections were obtained in the presence and absence of CORLUX for determination of unchanged cimetidine on Day 1 of Period 1 (single dose of cimetidine), on Day 1 of Period 3 (single dose of CORLUX in combination with a single dose of cimetidine). The following PK parameters were calculated from urine concentrations of unchanged cimetidine and the volume of urine: renal clearance (CLr), amount excreted from time 0 to 24 hours after dosing (Ae_{0-24}), and the percentage excreted in urine from time 0 to 24 hours after dosing ($\%Ae_{0-24}$).
Safety Assessment	Safety assessments included monitoring of adverse events (AEs), clinical laboratory tests, vital sign measurements, physical examinations, and 12-lead electrocardiograms (ECGs).
Statistical Methods	**Mifepristone:** The 90% CIs were computed on the ratio of the geometric least square means (GLSMs) of log-transformed Cmax and AUCs for mifepristone and its metabolites using an ANOVA model with treatment as a fixed effect and subject as a random effect. Equivalence for the parameters was determined if the 90% CIs were contained in the predefined interval of 0.80 to 1.25. The treatment comparisons were as follows: C/B, D/B, E/B, F/B, E/D, F/D, and F/E.

Results:

Effect of mifepristone on cimetidine:

Geometric mean values of pharmacokinetic parameters and the statistical comparisons of PK parameters of cimetidine by treatments are summarized in Table 25.

Table 25. Statistical comparisons of pharmacokinetic parameters of cimetidine by treatment

Treatment	Parameter	N	Geometric Mean	Treatment Comparison	Ratio of GLSM	90% CI
C	AUC_{0-inf}	15	24430			
E	AUC_{0-inf}	15	27061	E/C	1.11	1.05-1.16

Reference ID: 3072217

	AUC_{0-24}	20	63595	F/E	1.00	0.95-1.05
	Cmax	16	5397			
	Cmax	16	5686	E/C	1.05	0.94-1.19
	Cmax	16	5186	F/E	0.91	0.81-1.03
A	$\%A_{e0-24}$	16	55.5			
C	$\%A_{e0-24}$	16	50.5	C/A	0.91	0.78-1.06
E	$\%A_{e0-24}$	16	62.1	E/A	1.12	0.96-1.30
F	$\%A_{e0-24}$	16	58.8	F/A	0.16	0.91-1.23
				E/C	1.23	1.05-1.43
				F/E	0.95	0.81-1.10

Treatment A = single 800-mg cimetidine dose.
Treatment C = first 300-mg CORLUX dose of a multiple-dose regimen and a single 800-mg cimetidine dose.
Treatment E = multiple doses of CORLUX at 300 mg/day and a single 800-mg cimetidine dose.
Treatment F = multiple doses of CORLUX at 300 mg/day and multiple doses of cimetidine at 800 mg/day.
(Source: study report Table 11-17)

The comparisons were made for single dose pharmacokinetics of cimetidine in Period 3 when multiple doses of mifepristone were co-administered: the effect of the last dose compared with the first dose of mifepristone multiple dosing on cimetidine PK. The ratios of geometric least square means fell with 0.8-1.25 range. However, the results are not interpretable for the objective of the study.

The urine PK parameters used for the comparison between Treatment A and others are summarized in Table 26.

Table 26. Mean (CV) urine pharmacokinetic parameters of cimetidine

Parameter	Treatment A	Treatment C	Treatment E	Treatment F
N	20	20	20	20
A_{e0-24}	433.5 (13)	422.2 (24)	480.9 (22)	468.7 (31)
$\%A_{e0-24}$	54.2 (13)	52.8 (24)	60.1 (22)	58.6 (31)
CLr	NA	18.0 (31)	18.8 (21)	18.2 (35)

Treatment A = single 800-mg cimetidine dose.
Treatment C = first 300-mg CORLUX dose of a multiple-dose regimen and a single 800-mg cimetidine dose.
Treatment E = multiple doses of CORLUX at 300 mg/day and a single 800-mg cimetidine dose.
Treatment F = multiple doses of CORLUX at 300 mg/day and multiple doses of cimetidine at 800 mg/day.
(Source: study report Table 11-7)

The recoveries of cimetidine from the urine are less than 60% since urine samples were not collected for sufficient period of time.

Reviewer's analysis and comments:

It should be noted that the reference treatment (single dose of cimetidine without co-administration of mifepristone) was not used in statistical comparisons. The effect of mifepristone on the pharmacokinetics of cimetidine would be adequately assessed when Treatment A is used as a reference treatment. The comparison of Treatment C and A, which is reported by the sponsor, will give an estimated effect of the first dose of multiple doses of mifepristone on the single dose PK of cimetidine and the comparison of Treatment F and A will give an estimated effect of the last dose of multiple doses of mifepristone on the single dose PK of cimetidine. The sponsor conducted comparisons

Reference ID: 3072217

for the amount of excreted in the urine using Treatment A as the reference. However, it is also insufficient for reliable prediction on the drug interaction since the drug recovery was less ~60% or less. However, the main objective of the study is to evaluate the effect of cimetidine on mifepristone not the effect of mifepristone on cimetidine. Thus, the lack of information is not critical.

Effect of cimetidine on mifepristone:

Geometric mean values of pharmacokinetic parameters and the statistical comparisons of PK parameters of mifepristone by treatments are summarized in Table 27. Furthermore, the mean (SD) concentrations of mifepristone versus time profiles are depicted in Figure 24.

Table 27. Statistical comparisons of pharmacokinetic parameters of mifepristone by treatment

Treatment	Parameter	N	Geometric Mean	Treatment Comparison	Ratio of GLSM	90% CI
B	AUC_{0-24}	20	21488			
C	AUC_{0-24}	20	20953	C/B	0.98	0.85-1.12
B*	AUC_{0-inf}	20	63595			
D	AUC_{0-24}	20	34836	D/B	0.55	0.50-0.60
E	AUC_{0-24}	20	31613	E/B	0.50	0.45-0.55
F	**AUC_{0-24}**	**20**	**29491**	**F/B***	**0.46**	**0.42-0.51**
				E/D	0.91	0.87-0.94
				F/D	0.85	0.82-0.88
				F/E	0.93	0.90-0.97
B	Cmax	20	2141			
C	Cmax	20	1722	C/B	0.80	0.70-0.92
D	Cmax	20	2604	D/B	1.22	1.06-1.39
E	Cmax	20	2040	E/B	0.95	0.83-1.09
F	Cmax	20	1950	F/B	0.91	0.80-1.04
				E/D	0.78	0.72-0.86
				F/D	0.75	0.69-0.82
				F/E	0.96	0.88-1.04

AUC_{0-inf} following single dose is reference to AUC_{0-24} following multiple doses
Treatment B = single 300-mg CORLUX dose.
Treatment C = first 300-mg CORLUX dose of a multiple-dose regimen and a single 800-mg cimetidine dose.
Treatment D = multiple doses of CORLUX at 300 mg/day.
Treatment E = multiple doses of CORLUX at 300 mg/day and a single 800-mg cimetidine dose.
Treatment F = multiple doses of CORLUX at 300 mg/day and multiple doses of cimetidine at 800 mg/day.
(Source: study report Table 11-8)

The geometric least square mean (GLSM) ratio for AUC_{0-24} of mifepristone with versus without co-administration of a single dose of 800 mg cimetidine at steady state was 0.91 (CI 0.87-0.94). The geometric least square mean (GLSM) ratio for AUC_{0-24} of mifepristone with versus without co-administration of a single dose of 800 mg cimetidine at steady state was 0.78 (CI 0.72-0.86).

The GLSM ratio for AUC_{0-24} of mifepristone with versus without co-administration of a multiple doses of 800 mg cimetidine at steady state was 0.85 (CI 0.82-0.88). The GLSM ratio for AUC_{0-24} of mifepristone with versus without co-administration of a single dose of 800 mg cimetidine at steady state was 0.75 (CI 0.69-0.82).

Reference ID: 3072217

Based on the comparisons the sponsor made, the sponsor claims that there was no evidence effect of cimetidine on the pharmacokinetics of multiple doses of mifepristone. However, the study results should be carefully interpreted based on adequate comparisons (See reviewer's comments and analysis).

Reviewer's comments:

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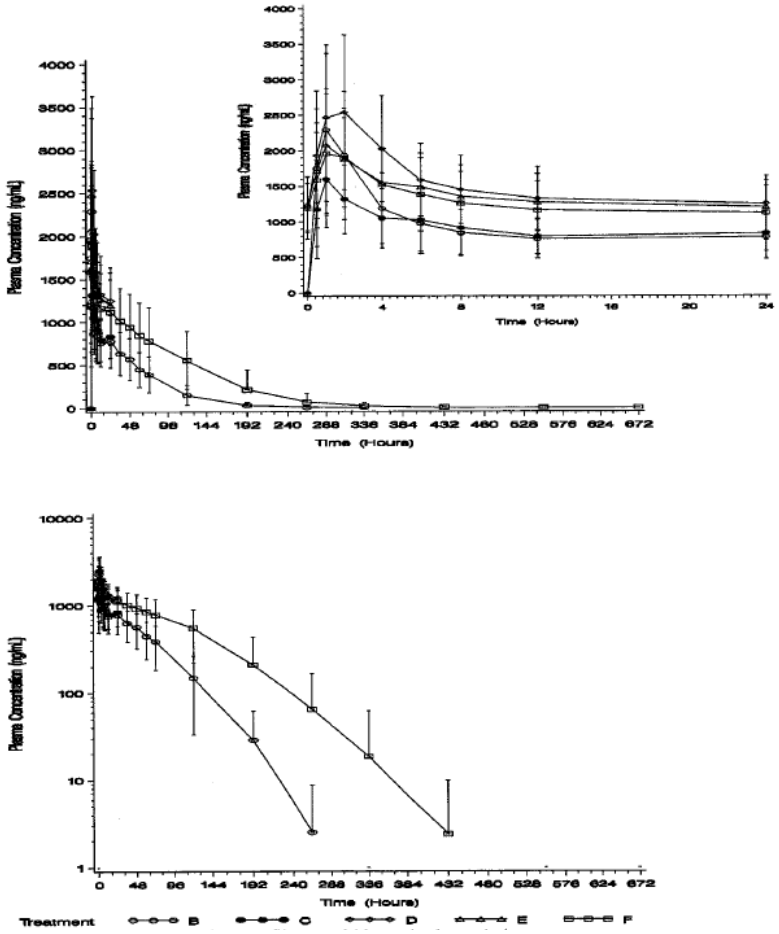


Treatment B = single 300-mg CORLUX dose.
Treatment C = first 300-mg CORLUX dose of a multiple-dose regimen and a single 800-mg cimetidine dose.
Treatment D = multiple doses of CORLUX at 300 mg/day.
Treatment E = multiple doses of CORLUX at 300 mg/day and a single 800-mg cimetidine dose.
Treatment F = multiple doses of CORLUX at 300 mg/day and multiple doses of cimetidine at 800 mg/day.

Figure 24. Mean concentrations of mifepristone versus time by treatment. Two plots in the linear scale are for Treatment B and Treatment F.

As shown in Figure 24, there is significant in the exposure of mifepristone between Treatments B and F. It is not fully reflected in Table 27 since the sponsor compared $AUC_{0\text{-inf}}$ of Treatment B and $AUC_{0\text{-}24}$ of Treatment F, and reported 0.46 for the GLSM ratio. This comparison is undesirable since the pharmacokinetics of mifepristone is

Reference ID: 3072217

nonlinear and time-dependent: AUC_{0-24} does not fully represent the effect of cimetidine on pharmacokinetics of mifepristone due to the time-dependent PK of mifepristone and its metabolites. Moreover, the comparison of AUC_{0-24} following multiple doses and AUC_{0-inf} following a single dose is not adequate for drugs with nonlinear PK.

Among all the comparisons reported in Table 27, comparisons of Treatment E to Treatment D and Treatment F to Treatment D are relevant to the effect of cimetidine on the pharmacokinetics of mifepristone; the effect of single dose of cimetidine on multiple dose PK of mifepristone at steady state and the effect of multiple doses of cimetidine on multiple dose PK of mifepristone at steady state. However, the effect of single dose of cimetidine on the single dose PK of mifepristone cannot be adequately evaluated from this study design. The sponsor reported the effects of single dose and multiple doses of cimetidine on the multiple dose PK of mifepristone by comparing Treatments E and F to Treatment F, respectively. As shown in the table, cimetidine administration does not seem to have any impact on exposure of mifepristone (Cmax decreased by 22~25%). The mechanism-based inhibition of mifepristone on its own metabolism, may not allow an adequate assessment of drug-interaction at steady state or the remaining capacity of metabolizing enzyme may not be sensitive to any influence by inhibitors.

The comparison between the Treatments of F and B was made for AUC_{0-24} to AUC_{0-inf} in the report while the figure for those treatments shows a drastic difference. Since AUC_{0-inf} comparison can be more valid when mifepristone PK is time-dependent, the reviewer conducted an independent analysis for the comparison for Treatments B and F and generated another comparison (Table 28).

Table 28. Statistical comparison of pharmacokinetic parameters of mifepristone and its metabolites following a singe dose of 300 mg mifepristone and following multiple doses of 300 mg/day of mifepristone co-administered with 800 mg of cimetidine (Reviewer's analysis)

Analyte	Parameter	Ratio	CI_90_Lower	CI_90_Upper
Mifepristone	AUC_{0-inf}	2.06	1.89	2.26
	Cmax	0.91	0.80	1.03
	Half-life	1.21	1.10	1.33
RU 42633	AUC_{0-inf}	1.85	1.68	2.03
	Cmax	0.90	0.79	1.02
	Half-life	1.27	1.10	1.46
RU 42698	AUC_{0-inf}	2.27	2.07	2.48
	Cmax	1.16	1.01	1.33
	Half-life	1.35	1.16	1.56
RU42848	AUC_{0-inf}	1.90	1.68	2.15
	Cmax	1.25	1.07	1.48
	Half-life	1.18	1.06	1.31

Although the results confirmed the significant increase in AUC when the two treatments were compared using AUC_{0-inf}, they do not reflect the sole effect of drug-drug interaction because the dosing regimen effect of mifepristone (single vs. multiple) is confounded.

Reference ID: 3072217

4.1.7 C-1073-16: DDI with Fluvastatin

Title: A Phase 1, Open-Label, Fixed-Sequence Study to Determine the Effect of Single and Multiple Oral Doses of CORLUX (mifepristone) on the Pharmacokinetics of a Single Oral Dose of Fluvastatin (a CYP2C9 probe) in Healthy Volunteers

<table>
<tr><td>Objectives</td><td>Primary:
• To determine the effect of the first and last oral doses of a multiple dose regimen of mifepristone on the pharmacokinetics of a single oral dose of fluvastatin administered to healthy volunteers</td></tr>
<tr><td>Study Design</td><td>Open-label, fixed-sequence, drug-drug interaction study in healthy volunteers. Subjects received a single oral dose of 40 mg fluvastatin (Lescol®) on 3 occasions: alone on Day 1 (Treatment A), at the same time as the first dose of mifepristone 1200 mg/day on Day 8 (Treatment B), and at the time of the seventh and last dose of mifepristone 1200 mg/day on Day 14 (Treatment C). There was a 7-day washout between the first 2 doses and a 6-day washout between the last 2 doses of fluvastatin. Following each dose of fluvastatin, serial blood sampling over 24 hours was performed for determination of fluvastatin plasma concentrations. Periodic individual blood samples for determination of plasma concentrations of mifepristone and its metabolites were also obtained.</td></tr>
<tr><td>Study population</td><td>Twenty healthy volunteers enrolled and 18 subjects completed the study. One subject failed to return for Treatment B and C in Period 2; another subject did not return for a follow-up visit after completion of the study. Therefore, the pharmacokinetic population consisted of 20 subjects for Treatment A and 19 subjects for Treatment B and C.</td></tr>
<tr><td>Treatments</td><td><table>
<tr><th>Treatment</th><th>Mifepristone</th><th>Fluvastatin</th><th>Day</th></tr>
<tr><td>A</td><td>None</td><td>40 mg single dose</td><td>1</td></tr>
<tr><td>B</td><td>1200 mg/day (first dose)</td><td>40 mg single dose</td><td>8</td></tr>
<tr><td>C</td><td>1200 mg/day (last dose)</td><td>40 mg single dose</td><td>14</td></tr>
</table></td></tr>
<tr><td>Investigational Drugs</td><td>Lescol® (fluvastatin sodium) 40 mg capsule, Novartis
Corlux™ (mifepristone) 300 mg tablet (lot 8K05)</td></tr>
<tr><td>PK Assessment</td><td>Plasma concentrations of fluvastatin were determined within 30 minutes prior to each fluvastatin administration and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose using a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) assay method by [redacted] (b) (4). The limit of detection was 0.5 ng/mL. Concentrations of mifepristone and its metabolites (RU 42633, RU 42698, and RU 42848) were determined on Days 8~9 (pre-dose and 24 hours post first dose) and prior to the last 3 days of the multiple dose regimen (Study Days 12~14). [redacted] (b) (4) determined plasma concentrations of the 4 analytes using a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) assay. The lower limit of</td></tr>
</table>

Reference ID: 3072217

	detection of this method was 10 ng/mL for each analyte. Pharmacokinetic parameters calculated included Tmax, Cmax, AUC_{0-24hr}, AUC_{0-t}, AUC_{0-inf}, k_{el}, $T_{½}$, and $\%AUC_{extrapolated}$. A linear mixed model for analysis of variance (ANOVA) was performed to test for differences in the PK parameters of fluvastatin between treatments. Ninety percent (90%) confidence intervals (CIs) were computed on the ratio of the least square means (LSM) of log-transformed Cmax, AUC_{0-24hr}, and AUC_{0-inf} for the comparison of the 2 test treatments (Treatments B and C) to the reference treatment (Treatment A), and for the comparison of the difference in fluvastatin PK after the first and last dose of mifepristone 1200 mg/day (Treatment B to Treatment C). Absence of a clinically relevant effect of single or multiple doses of mifepristone on the single dose PK of fluvastatin was concluded if there was less than a 50% increase or decrease in each parameter based on the CIs being between 0.67-1.50.
Safety Assessment	Safety was assessed by spontaneously reported adverse events (AEs), physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and routine clinical laboratory tests.

Results:

One of the subjects who completed the study vomited 45 minutes postdose on Day 14 (Treatment C) which was within twice the expected Tmax of both fluvastatin and mifepristone; therefore the sponsor performed the statistical analysis including and excluding the data for the subject. No differences were observed between the two analyses.

Pharmacokinetic parameters of fluvastatin following three treatments are summarized in Table 29.

Table 29. Summary of the pharmacokinetic parameters of fluvastatin (Source: Clinical Study Report Tables 14.2.4 through 14.2.6)

Reference ID: 3072217

Pharmacokinetic Parameters	Treatment A	Treatment B	Treatment C
	Mean ± SD (N)	Mean ± SD (N)	Mean ± SD (N)
C_{max} (ng/mL)	323 ± 157 (20)	559 ± 246 (19)	606 ± 358 (19)
T_{max}[a] (h)	0.532 (0.500, 1.02) (20)	1.00 (0.499, 3.01) (19)	2.04 (1.00, 3.10) (19)
K_{el} (1/h)	0.305 ± 0.103 (20)	0.255 ± 0.0870 (19)	0.223 ± 0.0778 (19)
$t_{1/2}$ (h)	2.51 ± 0.774 (20)	3.03 ± 1.04 (19)	3.44 ± 1.04 (19)
AUC_{0-24} (ng*h/mL)	449 ± 165 (20)	1400 ± 930 (19)	1890 ± 1560 (19)
AUC_{0-t} (ng*h/mL)	445 ± 164 (20)	1390 ± 932 (19)	1880 ± 1560 (19)
AUC_{0-inf} (ng*h/mL)	449 ± 166 (20)	1400 ± 933 (19)	1890 ± 1560 (19)
%AUCextrap	0.915 ± 0.413 (20)	0.608 ± 0.422 (19)	0.486 ± 0.272 (19)

Tmax is presented as median (minimum, maximum)
Treatment A: 40 mg fluvastatin alone (Day 1)
Treatment B: 40 mg fluvastatin with the first dose of mifepristone 1200 mg/day for 7 days (Day 8)
Treatment C: 40 mg fluvastatin with the last dose of mifepristone 1200 mg/day for 7 days (Day 14)

Table 30. Statistical analysis of fluvastatin pharmacokinetic parameters (Source: Clinical Study Report Tables 11.4.1.2)

Parameter	Geometric LS Means		Geometric Mean Ratio	Confidence Intervals (90% Confidence)
	B	A	B/A	
C_{max}	494.6	290.4	1.70	1.27–2.29
AUC_{0-24}	1126.3	421.5	2.67	2.05–3.48
AUC_{0-inf}	1127.9	421.7	2.67	2.05–3.49
	C	A	C/A	
C_{max}	510.4	290.4	1.76	1.31–2.36
AUC_{0-24}	1500.1	421.5	3.56	2.73–4.64
AUC_{0-inf}	1504.7	421.7	3.57	2.74–4.65
	B	C	B/C	
C_{max}	494.6	510.4	**0.97**	**0.72–1.31**
AUC_{0-24}	1126.3	1500.1	0.75	0.57–0.98
AUC_{0-inf}	1127.9	1504.7	0.75	0.57–0.98

Treatment A: 40 mg fluvastatin alone (Day 1)
Treatment B: 40 mg fluvastatin with the first dose of mifepristone 1200 mg/day for 7 days (Day 8)
Treatment C: 40 mg fluvastatin with the last dose of mifepristone 1200 mg/day for 7 days (Day 14)

Median Tmax of fluvastatin increased from 0.53 hr 1.00 hr following single dose administration of mifepristone and nearly quadrupled (from 0.53 hr to 2.04 h) following multiple dose administration of mifepristone compared to administration of fluvastatin alone. Increases in Cmax of fluvastatin following the first mifepristone dose (ratio 0.70, CI, 1.27-2.29) and the last mifepristone dose(ratio 0.76, CI, 1.31-2.36) were equivalent (i.e., less than a 50% change for Treatment B/C) as defined by CI within the predefined boundary of 0.67-1.50 (ratio, 0.97, CI 0.72-1.31). Increases in fluvastatin AUC_{0-inf} were

Reference ID: 3072217

greater following the last multiple dose of mifepristone (ratio, 3.57, CI, 2.74-.65) than following the first dose of mifepristone (ratio, 2.67, CI 2.05-3.49). Mean half-life (ty,) of fluvastatin appeared to increase slightly when administered with both the first dose (3.03 versus 2.51 h) and last dose of mifepristone (3.44 versus 2.51 h) as compared to fluvastatin alone, respectively. Mean (SD) trough concentrations of mifepristone on the fifth, sixth and seventh day of multiple dose administration were l730 (515), 1830 (595) and l830 (593) ng/mL, suggesting that steady-state conditions had been achieved

Conclusion:

The first and last multiple doses of mifepristone 1200 mg/day for 7 days produced 2.67-fold and 3.57 fold increase, respectively, in fluvastatin AUC_{0-24}. Single and multiple doses of mifepristone produced equivalent increases in the Cmax of fluvastatin (70% and 76%, respectively). Median Tmax doubled (0.53 to 1.00 hr) following a single dose of mifepristone and quadrupled (0.53 to 2.04 hr) following multiple doses of mifepristone. Mean half-life increased slightly following the first dose (21 %) and last dose of mifepristone (37%). The results suggest that mifepristone inhibited the metabolism of fluvastatin via CYP2C9.

Reviewer's comments: Since the half-life of fluvastatin is short, it is believed for the drug to be cleared almost completely at 24 hour pose dose. Thus, the sponsor's statistical analyses for $AUC_{0-24\ hr}$ among treatments were acceptable. However, the effect of mifepristone on the pharmacokinetics of fluvastatin should be based on the comparison between single-dose PK of fluvastatin with or without concomitant administration of multiple doses of mifepristone. Thus, the statistical comparison results between Treatment C versus Treatment A should be reflected in the label. Independent analysis by the reviewer was not conducted.

4.1.8 C-1073-20: Food Effect Study with 1200 mg Dose

Title: A Phase 1, Randomized, Open-Label Study to Determine the Effect of Food, and the Effect of Dose on the Pharmacokinetics of a Single Dose of CORLUX (mifepristone) in Healthy Volunteers

Objectives	Primary: • To determine the effect of a high-calorie, high-fat breakfast on the pharmacokinetics of a single 1200-mg oral dose of mifepristone Secondary: • To explore the effect of dose (single oral doses of 1200 mg versus 500 mg and 1200 mg versus 300 mg) on the pharmacokinetics of mifepristone/metabolites • To determine within-subject variability of the 3 mifepristone doses

Reference ID: 3072217

Study Design	Open-label, randomized, 3-period study. In first 2 periods, subjects received single oral doses of mifepristone 1200 mg under fasting conditions (Treatment A) and following a high-fat, high-calorie breakfast (Treatment B). In the third-period, subjects were received mifepristone as a single dose of either 600 mg (Treatment C) or 300 mg (Treatment D). There was at least 3-week washout between each dose of mifepristone. Following each dose, serial blood samples were obtained over 14 days (336 hours) to determine total plasma concentrations of mifepristone and its 3 active metabolites. A final safety evaluate was performed 3 weeks after the last dose of mifepristone. For each period, subjects were confined from the evening before dosing (Day 0) until after the 72-hour mifepristone blood sample was collected (Day 4). All subjects were required to return to the clinic for single blood sampling on Day 6, 8, 10, 12, and 15 of each period (± 2-hour window).
Study population	Twenty-four healthy subjects were enrolled, and 20 subjects completed the study. Four subjects discontinued due to work (n=1), family emergency (n=1) or positive urine drug screening results (n=2).
Treatments	

	Mifepristone	Fed/Fasting
TRT A	1200 mg (4 x 300 mg tablets)	Fasting
TRT B	1200 mg (4 x 300 mg tablets)	Fed
TRT C	600 mg (2 x 300 mg tablets)	Fasting
TRT D	300 mg (1 x 300 mg tablet)	Fasting

PK Assessment	Blood sampling for plasma analysis of mifepristone and its active metabolites (RU 42633, RU 42698, and RU 42848) was performed within 30 minutes prior to each dose and at 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 120, 168, 216, 264, and 336 hours post dose. (b) (4) [redacted] assayed all plasma samples using a validated LC/MS/MS assay. The lower limit of detection of this method was 10 ng/mL for each analyte. Pharmacokinetic parameters calculated included Tmax, Cmax, AUC_{last}, AUC_{0-72}, AUC_{0-inf}, and $T_{1/2}$. To determine the effect of food on a single 1200 mg dose of mifepristone, 90% confidence intervals (CIs) were computed on the ratio of the geometric least squares means of natural log-transformed Cmax, AUC_{last} and AUC_{0-inf} of mifepristone and its 3 active metabolites using a mixed-effect analysis of variance (ANOV A) model with sequence, treatment, and period as fixed effects, and subject (nested within sequence) as a random effect. Less than a 30% increase or decrease in the parameter was determined if the 90% CIs were contained in the interval 0.70 to 1.43. To determine the effect of dose, an ANOVA was performed on the data from Treatment A (1200 mg fasting), Treatment C (600 mg fasting), and Treatment D (300 mg fasting). The model was applied to the natural log-transformed, dose-normalized AUC_{last}, AUC_{0-inf}, and Cmax of

Reference ID: 3072217

	mifepristone and its 3 active metabolites with treatment and sequence as fixed effects and subject (nested within sequence) as a random effect. The least squares means and the difference of the least squares means of the natural log-transformed, dose-normalized AUC_{last}, $AUC_{0\text{-}inf}$, and Cmax for the treatments was back transformed to obtain the geometric means and ratios of geometric means on the raw data scale (Treatments CIA and D/A). 90% CIs for the ratios of the geometric means were calculated for the dose-normalized parameters AUC_{last}, $AUC_{0\text{-}inf,}$ and Cmax of mifepristone. Intra-subject CVs were also reported. A one-way ANOV A model (with a fixed-effect term for group, where group = A/C or A/D) was performed to test the differences between the A/C and A/D AUC ratios. Dose effect was also evaluated using a t-test, where the natural log-transformed AUC ratio was compared with the natural log-transformed dose ratio of Treatments A versus C or D (A/C and A/D). The p-values were reported for the comparison with a p-value < 0.05 indicating that the 2 comparisons were significantly different.
Safety Assessment	Safety assessments included vital signs, physical examinations, clinical laboratory testing, electrocardiograms (ECGs), and the monitoring of adverse events (AEs) and concomitant medication use.

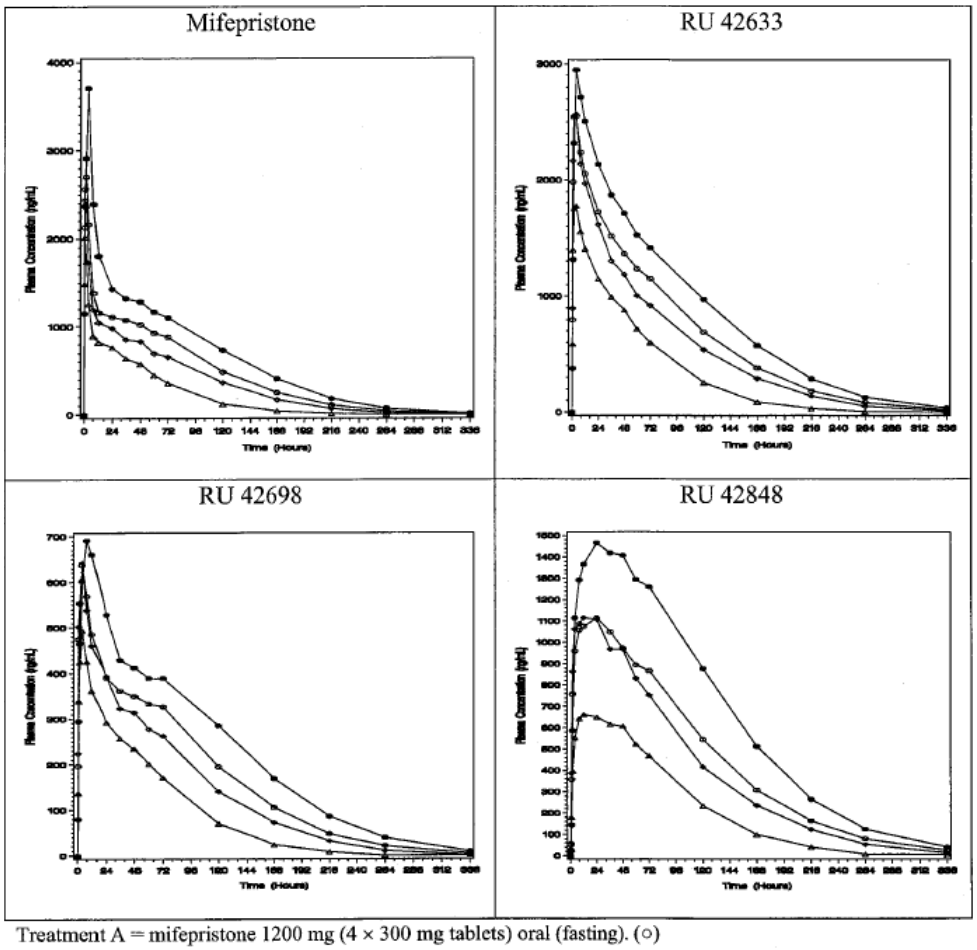
Results:

Mean plasma concentrations of mifepristone, RU 42633, RU 42698, and RU 42848 are presented by treatment on linear scales in Figure 25. Mean (CV) pharmacokinetic parameters for the four analytes are provided in Table 31.

Table 31. Mean (CV%) plasma pharmacokinetic parameters of mifepristone and its metabolites

Reference ID: 3072217

Mifepristone Parameters	Mifepristone Treatment Mean (CV)			
	1200 mg Fasting (N=24)	1200 mg Fed (N=22)	600 mg Fasting (N=10)	300 mg Fasting (N=11)
$AUC_{0\text{-last}}$ (ng•h/mL)	148759 (57)	204759 (46)	112927 (46)	66701 (46)
$AUC_{0\text{-}72}$ (ng•h/mL)	83275 (40)	110817 (34)	69218 (35)	49966 (33)
$AUC_{0\text{-inf}}$ (ng/mL)	152804 (57)	206633 (46)	114788 (45)	67776 (45)
C_{max} (ng/mL)	2995 (39)	3830 (35)	2735 (28)	2206 (40)
T_{max} (h)[a]	2.00 (0.50-4.00)	4.00 (0.50-8.00)	1.00 (0.50-2.00)	1.00 (0.50-4.00)
$t_{1/2}$ (h)	27.4 (30)	27.9 (33)	25.5 (35)	25.0 (34)
RU 42633 Parameter				
$AUC_{0\text{-last}}$ (ng•h/mL)	207816 (52)	269624 (39)	176190 (40)	107766 (48)
$AUC_{0\text{-}72}$ (ng•h/mL)	115629 (41)	139735 (32)	104659 (26)	75087 (45)
$AUC_{0\text{-inf}}$ (ng/mL)	209885 (52)	273314 (39)	177750 (40)	108569 (48)
C_{max} (ng/mL)	2729 (36)	3022 (30)	2709 (23)	1851 (48)
T_{max} (h)[a]	3.00 (1.00-8.03)	4.00 (4.00-8.00)	2.05 (1.00-4.00)	4.00 (1.00-4.00)
$t_{1/2}$ (h)	29.7 (36)	31.9 (35)	26.7 (34)	26.9 (37)
RU 42698 Parameter				
$AUC_{0\text{-last}}$ (ng•h/mL)	54435 (53)	71570 (48)	44976 (50)	28584 (56)
$AUC_{0\text{-}72}$ (ng•h/mL)	28536 (35)	34251 (33)	26345 (46)	19884 (37)
$AUC_{0\text{-inf}}$ (ng/mL)	55886 (52)	73165 (48)	45847 (49)	29696 (54)
C_{max} (ng/mL)	649 (25)	705 (27)	650 (34)	498 (33)
T_{max} (h)[a]	4.00 (1.00-12.00)	8.00 (4.00-12.07)	4.00 (1.00-8.00)	4.00 (1.00-8.00)
$t_{1/2}$ (h)	32.8 (30)	33.7 (30)	29.6 (36)	30.8 (37)
RU 42848 Parameter				
$AUC_{0\text{-last}}$ (ng•h/mL)	145160 (49)	213330 (33)	127252 (47)	71598 (48)
$AUC_{0\text{-}72}$ (ng•h/mL)	70648 (38)	95013 (34)	69030 (39)	41770 (47)
$AUC_{0\text{-inf}}$ (ng/mL)	147765 (50)	216544 (34)	128686 (46)	72835 (47)
C_{max} (ng/mL)	1184 (35)	1555 (33)	1196 (33)	740 (52)
T_{max} (h)[a]	24.00 (1.00-72.00)	36.00 (4.00-72.00)	12.00 (4.00-24.00)	36.03 (4.00-60.00)
$t_{1/2}$ (h)	34.9 (35)	35.3 (40)	36.0 (36)	32.5 (34)



Treatment A = mifepristone 1200 mg (4 × 300 mg tablets) oral (fasting). (○)
Treatment B = mifepristone 1200 mg (4 × 300 mg tablets) oral (fed). (●)
Treatment C = mifepristone 600 mg (2 × 300 mg tablets) oral (fasting). (◊)
Treatment D = mifepristone 300 mg (1 × 300 mg tablet) oral (fasting). (Δ)

Figure 25. Mean plasma concentration versus time profiles of mifepristone and its metabolites by treatment (Source: Clinical Study Report Figures 14.2.1. to 14.2.1.4)

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The statistical analysis for food effect is provided in Table 32. Furthermore, the sponsor provided the results of statistical analysis of pharmacokinetic parameters of three dose levels evaluated in this study (Table 33).

Table 32. Statistical analysis of pharmacokinetic parameters of mifepristone and its metabolites (Food effect)

Mifepristone Parameter	Mifepristone 1200 mg	N	Geometric Mean	Ratio of Geometric Means (B/A)	90% CI
$AUC_{0\text{-last}}$ (ng•h/mL)	Fast	23	132435.3		
	Fed	22	189042.4	1.43	1.24-1.65
$AUC_{0\text{-inf}}$ (ng•h/mL)	Fast	22	133881.3		
	Fed	22	190638.1	1.42	1.23-1.65
C_{max} (ng/mL)	Fast	24	2829.02		
	Fed	22	3663.23	1.29	1.16-1.45
RU 42633 Parameter					
$AUC_{0\text{-last}}$ (ng•h/mL)	Fast	23	186765.3		
	Fed	22	255147.5	1.37	1.19-1.56
$AUC_{0\text{-inf}}$ (ng•h/mL)	Fast	23	188372.5		
	Fed	22	258757.2	1.37	1.20-1.57
C_{max} (ng/mL)	Fast	24	2581.86		
	Fed	22	2949.18	**1.14**	**1.05-1.25**
RU 42698 Parameter					
$AUC_{0\text{-last}}$ (ng•h/mL)	Fast	23	49026.75		
	Fed	22	65773.59	1.34	1.17-1.54
$AUC_{0\text{-inf}}$ (ng•h/mL)	Fast	23	50362.71		
	Fed	22	67244.37	1.34	1.17-1.53
C_{max} (ng/mL)	Fast	24	631.15		
	Fed	22	689.39	**1.09**	**1.00-1.20**
RU 42848 Parameter					
$AUC_{0\text{-last}}$ (ng•h/mL)	Fast	23	131214.7		
	Fed	22	198906.6	1.52	1.31-1.76
$AUC_{0\text{-inf}}$ (ng•h/mL)	Fast	23	133163.4		
	Fed	22	201640.7	1.51	1.31-1.75
C_{max} (ng/mL)	Fast	24	1117.31		
	Fed	22	1475.19	1.32	1.20-1.45

Table 33. Statistical analysis of pharmacokinetic parameters of mifepristone and its metabolites (Dose effect)

Mifepristone Parameter	Mifepristone Dose (mg)	N	Geometric Mean	Ratio of Geometric Means (C/A or D/A)	90% CI	Intrasubject CV (%)
$AUC_{0\text{-last}}$/Dose (ng•h/mL/mg)	1200	20	109.36			26.44
	600	9	159.07	1.45	1.18–1.80	
	300	11	231.79	2.12	1.75–2.57	
$AUC_{0\text{-inf}}$/Dose (ng•h/mL/mg)	1200	19	110.94			26.14
	600	9	162.50	1.46	1.19–1.81	
	300	10	245.35	2.21	1.81–2.70	
C_{max}/Dose (ng/mL/mg)	1200	21	2.38			23.24
	600	10	4.35	1.83	1.53–2.19	
	300	11	7.02	2.96	2.50–3.50	
RU 42633 Parameter						
$AUC_{0\text{-last}}$/Dose (ng•h/mL/mg)	1200	20	152.74			24.05
	600	9	243.63	1.60	1.31–1.94	
	300	11	373.72	2.45	2.05–2.92	
$AUC_{0\text{-inf}}$/Dose (ng•h/mL/mg)	1200	20	154.43			24.10
	600	9	245.88	1.59	1.31–1.93	
	300	11	378.36	2.45	2.06–2.92	
C_{max}/Dose (ng/mL/mg)	1200	21	2.08			24.13
	600	10	4.15	2.00	1.66–2.40	
	300	11	5.81	2.80	2.35–3.33	
RU 42698 Parameter						
$AUC_{0\text{-last}}$/Dose (ng•h/mL/mg)	1200	20	41.85			24.39
	600	9	66.64	1.59	1.31–1.94	
	300	11	95.32	2.28	1.91–2.72	
$AUC_{0\text{-inf}}$/Dose (ng•h/mL/mg)	1200	20	42.94			24.15
	600	9	67.65	1.58	1.30–1.91	
	300	11	100.35	2.34	1.96–2.79	
C_{max}/Dose (ng/mL/mg)	1200	21	0.52			21.30
	600	10	1.06	2.04	1.73–2.40	
	300	11	1.60	3.05	2.62–3.57	
RU 42848 Parameter						
$AUC_{0\text{-last}}$/Dose (ng•h/mL/mg)	1200	20	110.74			27.74
	600	9	175.98	1.59	1.27–1.99	
	300	11	235.31	2.12	1.74–2.60	
$AUC_{0\text{-inf}}$/Dose (ng•h/mL/mg)	1200	20	112.67			27.82
	600	9	177.98	1.58	1.26–1.98	
	300	11	241.52	2.14	1.75–2.62	
C_{max}/Dose (ng/mL/mg)	1200	21	0.93			34.94
	600	10	1.84	1.98	1.52–2.57	
	300	11	2.20	2.37	1.84–3.04	

Food effect: A high-fat, high-calorie breakfast increased mifepristone Cmax and $AUC_{0\text{-inf}}$ by 29% and 42%, respectively, with increase for the metabolites ranging from 9 to 32% for Cmax and from 34% to 51% for $AUC_{0\text{-inf}}$.

Dose effect: Dose-normalized Cmax of mifepristone was 2.96- and 1.84-fold higher and dose-normalized $AUC_{0\text{-inf}}$ was 2.2- and 1.5-fold higher for the 300 mg and 300 mg doses, respectively, as compared to the 1200 mg dose. For the metabolites, increase in Cmax ranging from 1.98-fold to 3.05 fold higher and in $AUC_{0\text{-inf}}$ ranging from 1.58-fold to 2.45-fold higher were observed when comparing the 300 and 600 mg doses to the 1200 mg dose. Intra-subject variabilities (CVs) were 26% for $AUC_{0\text{-inf}}$ and 23% for Cmax.

Reviewer's comments: A significant food effect was observed which is in agreement with results obtained from other food effect studies.

Reference ID: 3072217

4.1.9 C-1073-27: Food Effect with 1200 mg/day Multiple Dose

Title: A Phase 1, Open-Label, Randomized, Crossover Study to Determined the Effects of Typical Meal (34% Fat) as Compared to Fasting on the Pharmacokinetics of CORLUX and its Metabolites Following Single and Multiple Daily Oral Doses of CORLUX in Healthy Volunteers

<table>
<tr><td>Objectives</td><td>Primary:
• To determine the effects of a typical meal (34% fat) on the pharmacokinetics of mifepristone and its metabolites following the first and subsequent multiple oral doses of mifepristone 1200 mg/day
Secondary:
• To determine the effects of a high-fat meal (50% fat) on the pharmacokinetics of mifepristone and its metabolites on mifepristone 1200 mg/day
• To explore the relationship, if any, between plasma concentrations of ghrelin (active and total), human growth hormone and plasma concentrations of mifepristone
• To determine the terminal elimination half-life of mifepristone and its metabolites following administration of mifepristone 1200 mg/day for 7 or 8 days under fasting or fed conditions</td></tr>
<tr><td>Study Design</td><td>Open-label randomized, 2-period, crossover study of the first and subsequent multiple doses of mifepristone 1200 mg/day administered daily under fasted and fed conditions. Subjects were randomly assigned in a 1:1 ratio to the sequence of regimens. Mifepristone 1200 mg/day was administered for 7 days in the fasting regimen and for 8 days in the fed regimen. Both regimens required daily overnight fasting. For the fasting regimen, subjects maintained the fast for 4 hours after dosing on Days 1 and 7 for 2 hours after dosing on Days 2 through 6. For the fed regimen, subjects consumed a typical breakfast (34% fat) before dosing on Days 1 through 7 and a high-fat breakfast (50% fat) before dosing on Day 8. There was a 3-week washout between periods.</td></tr>
<tr><td>Study population</td><td>Twenty-four subjects were enrolled and 22 subjects completed the study.</td></tr>
<tr><td>Treatments</td><td><table>
<tr><th></th><th>Mifepristone</th><th>Fed/Fasted</th><th>N</th></tr>
<tr><td>TRT A</td><td>1200 mg/day</td><td>Fasted</td><td>22</td></tr>
<tr><td>TRT B</td><td>1200 mg/day</td><td>Fed (34% fat)</td><td>24</td></tr>
<tr><td>TRT C</td><td>1200 mg/day</td><td>Fed (50% fed)</td><td>24</td></tr>
</table></td></tr>
<tr><td></td><td></td></tr>
<tr><td>PK Assessment</td><td>Serial blood sampling for plasma concentrations of mifepristone and its active metabolites (RU 42633, RU 42698, and RU 42848) was performed within 30 minutes before dosing and at 0.5, 1, 2, 4, 8, 12, and 24 hours after dosing on Days 1 and 7 of both regimens and Day 8 of the</td></tr>
</table>

Reference ID: 3072217

	fed regimen. In Period 1 only, subjects returned to the clinic on Days 11, 14, 17,20, and 23 (±24 hours each visit) for the collection of single PK blood samples for plasma concentrations of mifepristone and its active metabolites. In addition, blood samples for the determination of pre-dose plasma concentrations of mifepristone and its metabolites were collected on Days 5, 6, and 7. [redacted] (b) (4) assayed all plasma samples for mifepristone and the 3 active metabolites (RU 42633, RU 42698 and RU 42848) using a validated LC/MS/MS assay. The lower limit of detection of this method was 10 ng/mL for each analyte. Pharmacokinetic parameters calculated included Tmax, Cmax, AUC_{0-last} , AUC_{0-inf} , $T_{1/2}$, MRT, CL/F and Vd_{β}/F. Formal equivalence comparisons of pharmacokinetic parameters of the two populations were done using 90% confidence intervals. An analysis of variance was performed on the natural logarithms of the parameters with treatment, period, and sequence as fixed effects and subject as a random effect. Point estimates and 90% CIs for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale. Equivalence was determined if the 90% CIs were fully contained between 0.80-1.25.
Safety Assessment	Safety assessments included monitoring of adverse events (AEs), clinical laboratory tests, vital sign measurements, physical examinations, and 12-lead electrocardiograms (ECGs).

Results:

PD Assessment: The endpoints are not relevant to the indication of current submission.

PK Assessment: The pharmacokinetic parameters of mifepristone and its metabolites are summarized in Table 34.

Table 34. Mean (CV) plasma pharmacokinetic parameters of mifepristone and its metabolites

Reference ID: 3072217

		Parameter	Mifepristone 1200 mg/day - Mean (CV)		
			Fasting (N = 22)	Fed (34% Fat) (N = 24)	Fed (50% Fat) (N = 24)
MIFE	**Day 1**	AUC_{0-24} (ng•h/mL)	29837 (39)	41088 (33)	NA
		C_{max} (ng/mL)	2698 (37)	3428 (30)	NA
		T_{max} (h) median	1.0 (0.5, 4.0)	4.0 (0.5. 4.0)	NA
	Day 7/8	AUC_{0-24} (ng•h/mL)	47187 (38)	75428 (27)	76776 (26)
		C_{max} (ng/mL)	3439 (38)	5237 (28)	5048 (25)
		T_{max} (h) median	1.1 (0.5, 4.0)	4.0 (2.0, 8.0)	4.0 (2.0, 4.0)
		$t_{1/2}$ (h)	41.87 (42)[a]	[f]	65.74 (90)[c, f]
RU 42633	**Day 1**	AUC_{0-24} (ng•h/mL)	41312 (43)	47913 (28)	NA
		C_{max} (ng/mL)	2373 (38)	2666 (26)	NA
		T_{max} (h) median	2.0 (1.0, 8.0)	4.0 (2.0, 8.0)	NA
	Day 7/8	AUC_{0-24} (ng•h/mL)	42186 (35)	48858 (28)	49958 (28)
		C_{max} (ng/mL)	1998 (31)	2264 (30)	2331 (28)
		T_{max} (h) median	4.0 (2.0, 24.0)	8.0 (0.0. 12.1)	4.0 (0.5, 24.1)
		$t_{1/2}$ (h)	54.72 (60)[a]	[f]	56.99 (79)[d,f]
RU 42698	**Day 1**	AUC_{0-24} (ng•h/mL)	10722 (43)	12988 (34)	NA
		C_{max} (ng/mL)	593 (37)	667 (32)	NA
		T_{max} (h) median	4.0 (1.0, 8.0)	8.0 (1.0, 12.0)	NA
	Day 7/8	AUC_{0-24} (ng•h/mL)	13273 (40)	17601 (30)	18205 (30)
		C_{max} (ng/mL)	640 (39)	850 (30)	861 (30)
		T_{max} (h) median	4.0 (2.0, 12.0)	8.0 (0.0, 12.1)	8.0 (0.5, 24.1)
		$t_{1/2}$ (h)	59.77 (51)[b]	[f]	56.62 (44)[e,f]
RU 42848	**Day 1**	AUC_{0-24} (ng•h/mL)	20636 (37)	24508 (35)	NA
		C_{max} (ng/mL)	997 (37)	1220 (35)	NA
		T_{max} (h) median	12.0 (2.0, 24.4)	8.0 (4.0, 24.0)	NA
	Day 7/8	AUC_{0-24} (ng•h/mL)	32501 (27)	41571 (31)	43375 (31)
		C_{max} (ng/mL)	1465 (27)	1867 (31)	1967 (32)
		T_{max} (h) median	12.0 (0.0, 24.0)	8.0 (0.0, 24.0)	12.0 (0.0, 72.0)
		$t_{1/2}$ (h)	61.66 (54)[a]	[f]	69.19 (83)[d,f]

Abbreviations: CV, coefficient of variation; NA, not applicable.

[a] n=11
[b] n=10
[c] n=5
[d] n=4
[e] n=3
[f] $t_{1/2}$ was determined after 7 days of 34% fat and 1 day of 50% fat

Table 35. Statistical analysis of plasma pharmacokinetic parameters: primary endpoint (first and multiple doses)

Reference ID: 3072217

		Parameter	Mifepristone 1200 mg/day[a]	N	Geometric Mean	Ratio (B/A)	90% CI of the Ratio
MIFE	**Day 1**	AUC_{0-24} (ng•h/mL)	A	22	27286.24		
			B	24	39049.10	1.43	1.30–1.58
		C_{max} (ng/mL)	A	22	2476.68		
			B	24	3260.38	1.32	1.19–1.46
	Day 7	AUC_{0-24} (ng•h/mL)	A	22	44173.08		
			B	24	72765.84	1.65	1.52–1.79
		C_{max} (ng/mL)	A	22	3222.63		
			B	24	5038.79	1.56	1.41–1.74
RU 42633	**Day 1**	AUC_{0-24} (ng•h/mL)	A	22	37197.05		
			B	24	46215.48	1.24	1.11–1.39
		C_{max} (ng/mL)	A	22	2153.83		
			B	24	2586.17	1.20	1.08–1.33
	Day 7	AUC_{0-24} (ng•h/mL)	A	22	38968.55		
			B	24	47163.98	1.21	1.15–1.28
		C_{max} (ng/mL)	A	22	1866.34		
			B	24	2176.44	**1.17**	**1.11–1.22**
RU 42698	**Day 1**	AUC_{0-24} (ng•h/mL)	A	22	9775.10		
			B	24	12219.69	1.25	1.14–1.37
		C_{max} (ng/mL)	A	22	556.75		
			B	24	634.06	**1.14**	**1.04–1.24**
	Day 7	AUC_{0-24} (ng•h/mL)	A	22	12548.98		
			B	24	16868.83	1.34	1.27–1.43
		C_{max} (ng/mL)	A	22	607.95		
			B	24	814.49	1.34	1.26–1.43
RU 42848	**Day 1**	AUC_{0-24} (ng•h/mL)	A	22	19007.82		
			B	24	23419.86	1.23	1.06–1.44
		C_{max} (ng/mL)	A	22	917.85		
			B	24	1165.15	1.27	1.10–1.47
	Day 7	AUC_{0-24} (ng•h/mL)	A	22	31013.95		
			B	24	39927.35	1.29	1.20–1.38
		C_{max} (ng/mL)	A	22	1392.92		
			B	24	1792.86	1.29	1.21-1.37

Bold indicates CI within the predefined boundary of 0.80-1.25 (ie, less than a 20% change).
Abbreviation: CI, confidence interval; MIFE: mifepristone. Source: End-of-Text Tables 14.2.3.1. – 14.2.3.4
[a] Treatment A = fasting for 7 days; Treatment B = fed for 7 days (34% fat breakfast).

Conclusions and reviewer's comments:

Mean Cmax and AUC_{0-24hr} of mifepristone increased ~ 32% and 43%, respectively, after the first dose of 1200 mg mifepristone and 56% and 65%, respectively, after 7 days of mifepristone 1200 mg/day under fed conditions (34% fat breakfast) compared with fasting condition. After an eighth day of dosing with mifepristone 1200 mg/day given

Reference ID: 3072217

with a 50% fat breakfast, Cmax and $AUC_{0\text{-}24hr}$ increased by 52% and 68%, respectively, compared with fasting condition. Cmax and $AUC_{0\text{-}24hr}$ following mifepristone dose with 50% fat meal were similar to those with 34% fat breakfast. There is a significant food effect but it was not dependent on the meal content.

4.1.10 C-1073-12: Food Effect Study with 600 mg Dose

Title: Phase 1, Open-Label, Crossover Study of the Pharmacokinetics of Single Doses of Orally Administered CORLUX (mifepristone) in Fed versus Fasting State in Healthy Volunteers

Objectives	To determine the pharmacokinetics and safety of a single 600 mg dose of mifepristone administered under fed versus fasting state to healthy subjects
Study Design	This was an open-label, randomized, 2-way crossover, food-effect study. Subjects were stratified by age and gender and were assigned to receive in random order single doses of 600 mg of mifepristone following a standardized high-fat, high-calorie breakfast (Treatment A) and following an overnight fast (Treatment B). A 4-week washout period separated the 2 dosing periods. For 48 hours following each dose, subjects were confined and serial blood samples were taken for pharmacokinetic analyses of mifepristone and its active metabolites (RU 42633, RU 42698, and RU 42848). Subjects returned on Days 6, 11, and 15 for additional blood draws for pharmacokinetic analyses and safety assessments. A final safety evaluation was performed 4 weeks after the last dose.
Study population	50 healthy subjects were enrolled and 49 subjects were included in pharmacokinetic analysis.
Treatments	

Treatment	Dose	Strength	Fed/Fasted
A	600 mg	300 mg × 2	Fed
B	600 mg	300 mg × 2	Fasted

PK Assessment	Blood sampling for plasma PK analysis was taken within 1 hour prior to dosing and at 0.5, 1, 2, 4, 8, 12, 24, 48, 120, 240, and 336 hours post dose with a ± 24 hour window allowed for the last 3 time points. [redacted] (b) (4) determined plasma concentrations of mifepristone and its 3 active metabolites (RU 42633, RU 42698 and RU 42848) using a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) assay method. The lower limit of detection of this method was 10 ng/mL for each analyte. Pharmacokinetic parameters calculated included Tmax, Cmax, AUC_{last}, AUC_{inf}, $T_{1/2}$, MRT, CL/F, and Vd_{β}/F. Formal equivalence comparisons of the log-transformed pharmacokinetic parameters were performed for AUC_{inf} and Cmax using 90% CIs. Equivalence was determined if the CIs were contained within a predefined boundary of 0.80-1.25.

Reference ID: 3072217

Safety Assessment	Safety assessments included vital signs, physical examinations, clinical laboratory testing, electrocardiograms (ECGs), and the monitoring of adverse events (AEs) and concomitant medication use.

Results:

One subject vomited 5 minutes after taking the 600-mg dose under fed conditions (high fat, high calorie breakfast) and was discontinued from the study; the subject did not receive the treatment under fasting conditions. Forty nine subjects were included in the pharmacokinetic analysis and the pharmacokinetic parameters are described in Table 36.

Table 36. Pharmacokinetic parameters of mifepristone and its metabolites following a single dose of 600 mg of mifepristone under fasting or fed conditions (N=49)

	Analyte	T_{max}[a] (h)	C_{max} (ng/mL)	AUC_{inf} (ng*h/mL)	$t_{½}$ (h)
Fasting (N = 49)	Mifepristone	2.0	2,560 ± 1,139	123,217 ± 75,294[b]	40.8 ± 11.2[b]
	RU 42633	2.1	2,384 ± 926	187,555 ± 111,188[c]	43 ± 13[c]
	RU 42698	4.0	603 ± 257	49,414 ± 35,651[d]	51 ± 15[d]
	RU 42848	12.0	990 ± 456	127,456 ± 72,806[e]	47 ± 14[e]
Fed (N = 49)	Mifepristone	4.0	2,839 ± 743	145,436 ± 57,519	40.8 ± 12.7
	RU 42633	4.0	2663 ± 668	224,550 ± 89,212	42 ± 12
	RU 42698	8.0	637 ± 178	56,459 ± 25,864	47 ± 12
	RU 42848	24.0	1,205 ± 373	153,812 ± 53,087[f]	45 ± 15[f]

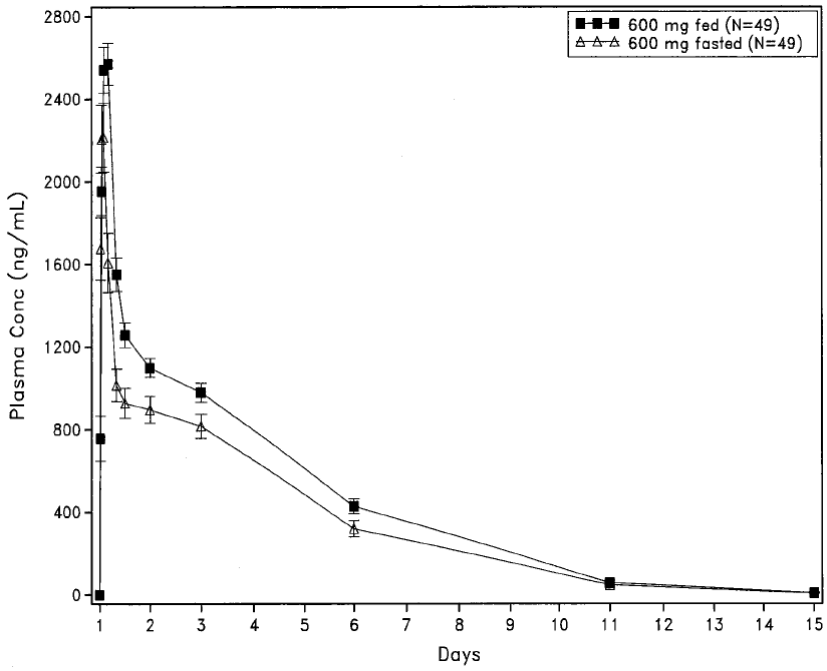

Figure 26. Mean (SE) plasma concentrations of mifepristone vs., time profile following a single dose of mifepristone under fed or fasted conditions

Table 37. Statistical analysis of pharmacokinetic parameters of mifepristone and its metabolites following a single dose of 600 mg of mifepristone under fasting or fed conditions

Reference ID: 3072217

Analyte	Parameter	Treatment	N	LS Mean	Ratio		*P* value		
						90% CI	Treatment	Period	Sequence
Mife-pristone	$AUC_{0\text{-}inf}$ (ng.h/mL)	fed	49	134083	1.29	1.15-1.45	< 0.001	0.612	0.210
		fasting	40	103905					
	C_{max} (ng/mL)	fed	49	2735	1.19	1.06-1.33	0.015	0.652	0.145
		fasting	49	2306					
RU 42633	$AUC_{0\text{-}inf}$ (ng.h/mL)	fed	49	206736	1.28	1.15-1.42	< 0.001	0.784	0.282
		fasting	45	161896					
	C_{max} (ng/mL)	fed	49	2582	1.17	1.05-1.31	0.016	0.751	0.151
		fasting	49	2201					
RU 42698	$AUC_{0\text{-}inf}$ (ng.h/mL)	fed	49	50786	1.24	1.11-1.40	0.003	0.565	0.092
		fasting	42	40804					
	C_{max} (ng/mL)	fed	49	609	**1.11**	**1.00-1.22**	0.091	0.834	0.080
		fasting	49	551					
RU 42848	$AUC_{0\text{-}inf}$ (ng.h/mL)	fed	46	144221	1.29	1.15-1.46	< 0.001	0.787	0.432
		fasting	44	111399					
	C_{max} (ng/mL)	fed	49	1148	1.31	1.15-1.49	0.001	0.531	0.555
		fasting	49	880					

Time to reach the maximum concentration of mifepristone is delayed with food from 2 to 4 hours after dosing. Mean $AUC_{0\text{-}inf}$ and Cmax under fed conditions were 29% (CI, 1.15-1.45) and 19% (CL, 1.06-1.33) higher than those under fasted conditions. Plasma concentrations for both treatments declined at a similar rate with $T_{1/2}$ of 40.8±12.7 hours and 40.8±11.2 hours under fed and fasted conditions, respectively. The mean (SD) apparent clearance (CL/F) of 4.9 (2.3) L/hour and mean apparent volume of distribution (Vd_{β}/F) of 269 (106) L were lower under fed conditions than under fasted conditions (6.6 (3.8) L/hour and 364 (180) L, respectively). Food did not have significant effect on the pharmacokinetics of mifepristone and its metabolites including elimination half-lives. Slight delay in Tmax has been observed.

Reviewer's comments: Food increase Cmax of mifepristone by 19% and AUC by 29%. Similar food effects were observed for metabolites as well.

4.1.11 C-1073-22: Bioavailability Comparison for Three Formulations

Title: A Phase 1. Open-Label, Randomized Three-Way Crossover Study of the Effects of Formulation and Dissolution Rate on the Pharmacokinetics of CORLUX Following a Single 300 mg Dose of CORLUX (mifepristone) in Healthy Volunteers

Objectives	Primary: • To evaluate the effect of formulation differences as defined by *in vitro* dissolution rate on the pharmacokinetics of mifepristone
Study Design	Open-label randomized, three-period, crossover study in healthy subjects. Subjects received in random order three single doses of mifepristone 300 mg from different manufacturing lots under fasting conditions: original formulation (Treatment A), revised formulation with

Reference ID: 3072217

<table>
<tr><td></td><td>fast-release in vitro dissolution (Treatment B), and revised formulation with slow-release in vitro dissolution (Treatment C). There was a two-week washout between each dose of mifepristone. Following each dose, serial blood samples were obtained over 96 hours to determine total plasma concentrations of mifepristone. A final safety evaluation was performed 2 weeks after the last dose of mifepristone. For each period, subjects were confined from the evening prior to dosing (Day 0) until the 96-hour blood sample was taken (Day 5)</td></tr>
<tr><td>Study population</td><td>15 healthy volunteers were enrolled.</td></tr>
<tr><td>Treatments</td><td><table><tr><th>Treatment</th><th>Formulation</th><th>Dose</th></tr><tr><td>TRT A</td><td>Original Formulation</td><td>300 mg</td></tr><tr><td>TRT B</td><td>Revised, fast-release</td><td>300 mg</td></tr><tr><td>TRT C</td><td>Revised, slow-release</td><td>300 mg</td></tr></table></td></tr>
<tr><td>PK Assessment</td><td>Blood samples for determination of mifepristone plasma concentrations were taken within 30 minutes prior to each dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 84, and 96 hours. (b) (4) assayed all plasma samples for mifepristone only (i.e., no metabolites) using a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) assay. The lower limit of detection of this method was 10 ng/mL.
Pharmacokinetic parameters calculated included Tmax, Cmax, AUC_{last}, $AUC_{0\text{-}72\ hr}$, $AUC_{0\text{-}96hr}$, $AUC_{0\text{-}120\ hr}$, $AUC_{0\text{-}inf}$ and $T_{1/2}$. Formal equivalence comparisons of pharmacokinetic parameters around within-subject differences between treatments A versus B, A versus C and B versus C were performed using 90% confidence intervals using log-transformed pharmacokinetic parameters of mifepristone. Less than a 30% increase or decrease in the parameter was determined if the 90% CIs were contained within the interval 0.70 to 1.43.</td></tr>
<tr><td>Safety Assessment</td><td>Safety was assessed by spontaneously reported adverse events, physical examinations, and routine clinical laboratory tests.</td></tr>
</table>

Results:

The mean (SD) mifepristone pharmacokinetics are summarize in Table 38.

Table 38. The mean (SD) mifepristone pharmacokinetics following Treatments A, B and C

Reference ID: 3072217

Treatment		T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{0-72} (h*ng/mL)	AUC_{0-120} (h*ng/mL)	AUC_{inf} (h*ng/mL)	Half-Life (h)
A	N	15	15	15	15	15	14	14
	Mean	4.50	1923	47838	41607	51930	57552	29.74
	SD	12.05	950	21631	17665	24724	32863	10.32
	CV%	267.7	49.4	45.2	42.5	47.6	57.1	34.7
B	N	15	15	15	15	15	15	15
	Mean	2.57	2057	50289	43710	54463	63915	32.09
	SD	5.94	837	23022	18151	26897	39820	16.93
	CV%	231.4	40.7	45.8	41.5	49.4	62.3	52.8
C	N	15	15	15	15	15	15	15
	Mean	1.43	2074	51505	44778	55869	66292	32.28
	SD	0.78	841	24214	18946	28523	44443	16.45
	CV%	54.1	40.6	47.0	42.3	51.1	67.0	51.0

Formulation A = Original formulation, B = Revised formulation, fast release, C = Revised formulation, slow release.
Source: Clinical Study Report Table 7.

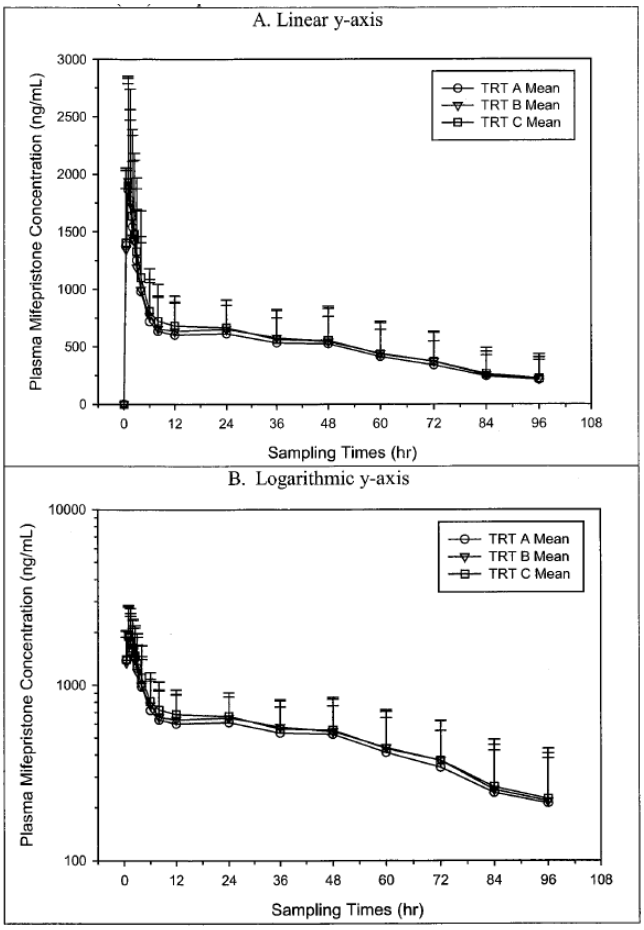

Figure 27. Mean (SD) concentrations of mifepristone versus time following three formulations of mifepristone 300 mg

The statistical comparisons of plasma mifepristone pharmacokinetic parameters are provided in table below.

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Reference ID: 3072217

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**

Bold indicates CI within predefined boundary of 0.70 to 1.43
Source: Clinical Study Report Tables 8-10

The 90% confidence intervals around the ratio of geometric means for PK parameters indicated that all AUC parameter were compared. Cmax values for treatments B and C were 17% and 15% greater, respectively, than for treatment A as reflected by the upper bound of the 90% CIs being outside the reference interval (CIs, B/A of 0.85-1.61, CIA 0.88-1.49). Cmax values for Treatments Band C were considered equivalent as the CI was fully contained within the predefined boundary (CI, 0.76-1.27) by the sponsor.

Reviewer's comments: The predefined boundary for CI was not acceptable; however, this is not critical since the to-be-marketed formulation was used in Phase 3 clinical trial.

4.1.12 C-1073-425: Multiple dose study at 600 mg/day to assess effects on high-density lipoproteins

Title: A Randomized, Placebo-Controlled Study to Evaluate the Effects of Mifepristone on HDL-Cholesterol Levels and HDL Functionality in Healthy Volunteers

Objectives	• To determine the effect of mifepristone on high-density lipoprotein-cholesterol (HDL-C) levels as determined by several complementary techniques and to examine HDL particle functionality in healthy postmenopausal female volunteers taking 600 mg of mifepristone/day
Study Design	This was a 14-week, randomized, double-blind, placebo-controlled study in 30 healthy volunteers. After up to 2 weeks of screening, subjects were randomized to mifepristone or matching placebo in a 2:1 ratio to receive 6 weeks of study treatment followed by a 6-week period off from study drug. All subjects were evaluated at Screening (Days -14 to -1) and Study Days 1, 8, 15, 29, 43, and 84. Lipid levels, apolipoprotein levels, HDL functionality, and relevant hormone levels were assessed at Days 1, 15, and Day 43. (Blood draws for standard lipid panels were done at Screening and Days 1, 15, 43, and 84).
Study population	Thirty-nine healthy postmenopausal female volunteers were enrolled. The subjects were 45 to 65 years of age, with normal liver function, euthyroid status, baseline serum HDL-C level > 40 mg/dL, and triglyceride level 0:200 mg/dL, and not concomitantly taking lipid-

Reference ID: 3072217

<table>
<tr><td></td><td>reducing drugs or other drugs known to interfere with lipid metabolism.</td></tr>
<tr><td>Treatments</td><td><table><tr><th>Treatment</th><th>Dose</th></tr><tr><td>TRT A</td><td>600 mg (300 mg × 2)</td></tr><tr><td>TRT B</td><td>Placebo</td></tr></table></td></tr>
<tr><td>PD Assessment</td><td>Mechanism measures:

Criteria for evaluation of effects of mifepristone on HDL-C: The change from baseline to Week 6 for the following parameters:
• Lipid fractions, including total cholesterol, HDL-C, high density lipoprotein cholesterol, low-density lipoprotein-cholesterol (LDL-C), triglycerides by ultracentrifugation (beta quantification) and standard lipid assay
• Lipoprotein subclass analysis by ion mobility (1M)
• Apolipoproteins: AI, AII, and B

The subject samples were also evaluated for:

• Cholesterol efflux from macrophages
• HDL speciation measured by electrophoresis gels
• Esterification/transfer studies (i.e., lecithin-cholesterol acetyltransferase (LCAT) and cholesterol ester transfer protein (CETP) activity
• Testosterone (including total, bioavailable, and free fractions), sex hormone binding globulin (SHBG), estradiol, estrone, luteinizing hormone (LH), follicle stimulating hormone (FSH)
• Fasting insulin and plasma glucose</td></tr>
<tr><td>Safety Assessment</td><td>Safety was also assessed by spontaneously reported adverse events, vital signs, physical examinations, routine clinical laboratory tests, electrocardiograms, transvaginal ultrasounds (subjects with intact uterus), and complete eye examinations. If a subject had abnormal findings on eye examinations (except for correctable visual acuity) at screening, she did not have additional eye examinations but underwent all other study procedures.</td></tr>
</table>

Results:

Table 39. Day 1 (Baseline) mean (SD) concentration and mean change from baseline in lipoprotein subclass particles at days 15 and 43, by treatment group (without imputation)

Reference ID: 3072217

Lipoprotein Subclass / Day	Mifepristone			Placebo	
	n	Baseline (n=20)	Change	Baseline (n=10)	Change
Total HDL		8557.3 (2011.9)		9254.8 (4318.6)	
Day 15	16		-2136.0 (2223.9)		-42.1 (3871.2)
Early term.	6		-2460.8 (2153.1)		----
Day 43	14		-1988.9 (1776.5)		+483.2 (2520.2)
HDL_{3+2a}		5548.9 (1267.3)	----	6465.2 (3173.4)	
Day 15	16		-469.7 (1636.5)		-398.0 (3588.4)
Early term.	6		-709.6 (1886.8)		----
Day 43	14		-288.1 (1388.4)		+161.6 (1492.5)
HDL_{2b}		3008.4 (1245.4)		2789.5 (1633.5)	
Day 15	16		-1666.3 (1046.3)		+355.9 (697.1)
Early term.	6		-1751.3 (460.2)		----
Day 43	14		-1760.8 (1097.3)		+321.7 (1402.0)
LDL peak diam. (Å)		226.1 (5.4)		225.1 (7.4)	
Day 15	16		-2.4 (4.3)		+0.9 (3.9)
Early term.	6		+0.4 (5.9)		----
Day 43	14		-2.5 (4.8)		+1.1 (4.8)

The values for total HDL particle concentration (i.e., the sum of HDL_{3+2a} and HDL_{2b} particle concentrations) for the mifepristone group show a pronounced drop from baseline by Day 15 that is sustained through Day 43. In the mifepristone group, a 23.3% overall decline in the mean level of total HDL particle concentration was observed at Day 43. As shown in Table 39, the mean change from baseline total HDL particle concentration at Day 43 in the mifepristone group was a decrease of 1988.9 nmol/L (23.3%), whereas the placebo group showed a mean increase of 483.2 nmol/L (5.2%). The difference between the mean changes in the two groups (mifepristone minus placebo) was 2472.1 nmol/L (95% CI: -4286.1, -658.1; p=0.010). The decrease in HDL_{3+2a} was less than that for HDL_{2b} (overall mean decline for HDL_{2b} of 55.4% vs. 5.2% for HDL_{3+2a}); the decline in the larger HDL_{2b} accounted for 94% of the mean change in total HDL particle concentration.

There was a statistically insignificant trend toward a decrease in peak diameter of LDL particles with mifepristone treatment.

Conclusions:

In the present study, mifepristone administered at 600 mg/day to 20 postmenopausal women produced a significant decrease in HDL-C, which was mostly due to reduction in the concentration of large, cholesterol-enriched HDL_{2b} particles rather than smaller HDL_{3+2a} particles. The results indicate the potential of mifepristone for the treatment effect in reducing HDL-C.

Reviewer's comments: The PD endpoints studied in the study are among many secondary endpoints of Cushing's syndrome. The statistical significance in HDL-C reduction was observed seem to be clinically meaningful for the proposed indication, Cushing's syndrome.

Reference ID: 3072217

4.1.13 Summary of *In Vitro* Studies

Study C-1073-PK-002: In Vitro Evaluation of the Binding of Mifepristone and Three Metabolites to Human Plasma Proteins

From Corcept-sponsored equilibrium dialysis studies, binding of mifepristone and its three active metabolites to human plasma proteins was ~99.2% for mifepristone, 98.9% for RU 42633, 97.8% for RU 42698, and 96.1% for RU 42848 with binding being only slightly concentration-dependent. The summary of protein binding characteristics of mifepristone and its metabolites are summarized in Table 40. The control drug used in this protein binding study was salicylic acid.

Table 40. Determination of equilibrium time of mifepristone and metabolite in pooled human plasma

Test	Time	Bound*		Free*		% Recovery		% Binding	
Article	h	ng/mL	% CV	ng/mL	% CV	Average	% CV	Average	% CV
C-1073	ctrl	10432	7.1					100.0	
	1	9705	3.9	36.8	34.6	93.7	10.1	99.6	0.15
	2	9514	3.7	74.2	33.9	92.3	9.7	99.2	0.29
	3	9343	14.6	96.5	24.7	91.2	19.3	98.9	0.40
	4	9966	6.3	103.7	19.5	97.0	12.6	99.0	0.26
	5	10153	2.6	116.7	23.0	98.8	9.3	98.9	0.29
RU 42633	ctrl	10456	0.9					100.0	
	1	9917	1.6	98.7	19.4	95.8	0.4	99.0	0.20
	2	10460	1.7	164.6	15.6	98.9	0.9	98.5	0.21
	3	9606	11.3	208.1	22.7	98.8	2.0	97.8	0.71
	4	9684	3.0	263.6	5.9	97.0	0.6	97.4	0.07
	5	10165	12.7	273.2	4.6	102.6	7.6	97.4	0.21
RU 42698	ctrl	11056	10.8					100.0	
	1	9900	14.1	141.3	15.4	90.7	2.7	98.6	0.41
	2	9932	10.0	305.2	0.2	92.6	1.0	97.0	0.28
	3	10033	0.6	352.1	10.0	94.5	10.4	96.6	0.34
	4	10268	7.1	386.2	2.9	97.3	17.2	96.4	0.15
	5	10314	10.3	410.5	3.8	97.0	0.7	96.2	0.24
RU 42848	ctrl	10626	7.7					100.0	
	1	9719	7.0	207.8	9.4	93.4	0.7	97.9	0.05
	2	9882	8.2	355.4	3.7	96.3	0.0	96.5	0.40
	3	9548	14.2	408.3	3.9	94.5	20.2	95.9	0.41
	4	9177	4.4	468.8	2.1	91.2	10.8	95.1	0.30
	5	9260	3.6	500.2	7.8	92.3	10.7	94.9	0.20

Study C-1073-PK-003 & Study C-1073-PK-004: Determination of the Inhibition Potential (Ki) of C-1073, RU42633, RU 42698, and RU 42848 Using Human Liver Microsomes

Study C-1073-PK-004 was conducted in May 2005 and reported IC_{50} for mifepristone and its metabolites for selected isoforms from incubation with human liver microsomes in the presence and absence of each analyte. Inhibitory potential was characterized as low, medium, or high based on the IC_{50} values (see Table 41). The sponsor concluded

Reference ID: 3072217

"medium" inhibitory effects of mifepristone and/or its metabolites for CYP2A6, CYO2C8, CYP2C9, CYP2C19, and CYP3A4.

The conclusion of Study C-1073-003 also included that mifepristone had a low inhibitory effect on CYP3A4 and other isoforms because it showed IC_{50} > 10 µM to CYPIA2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2El, CYP3A4. The results were reported in the study report of C-1073-PK-003, dated to December 2005.

Table 41. Summary of inhibition assays (Source: C-1073-004)

Isoform	Probe Substrate	C-1073 IC_{50} (μM)	RU 42633 IC_{50} (μM)	RU 42698 IC_{50} (μM)	RU 42848 IC_{50} (μM)	IC_{50} Positive Control (μM)
CYP1A2	Phenacetin	NI	NI	>50	NI	6.5
CYP2A6	Coumarin	>50	>50	8.5	>50	1.6
CYP2B6	Buproprion	NI	NI	>10	>50	5.8
CYP2C8	Paclitaxel	8.6	3.5	>10	6.7	1.9
CYP2C9	Diclofenac	>10	>10	3.0	>10	0.24
CYP2C19	(S)-Mephenytoin	>10	NI	8.5	>50	5.8
CYP2D6	Dextromethorphan	>10	>50	>10	>10	0.082
CYP2E1	Chlorzoxazone	NI	NI	NI	>50	0.82
CYP3A4	Midazolam	9.3	8.6	8.7	>10	0.013
CYP3A4	Nifedipine	>10	>10	>50	>10	0.11
CYP3A4	Testosterone	>10	8.1	>10	>10	0.12

Table 42. Summary of Ki and IC_{50} (Source: C-1073-003)

Isoform	Probe Substrate	Compound	IC_{50} (μM)	K_i (μM)	Assay Summary Sheet, page
CYP2A6	Coumarin	Tranylcypromine	1.6	0.3 – 0.8	A2
CYP2A6	Coumarin	RU 42698	8.5	2.5 – 10.0	D2
CYP2C8	Paclitaxel	Quercetin	1.9	1.0 – 3.0	A3
CYP2C8	Paclitaxel	C-1073	8.7	12 - 18	B2
CYP2C8	Paclitaxel	RU 42633	3.5	3.0 – 7.0	C2
CYP2C8	Paclitaxel	RU 42848	6.7	6.0 – 8.5	E2
CYP2C9	Diclofenac	Sulfaphenazole	0.24	0.1	A4
CYP2C9	Diclofenac	RU 42698	3.0	1.0 – 3.0	D3
CYP2C19	*S*-Mephenytoin	N-Benzylnirvanol	5.8	2.5 – 3.5	A5
CYP2C19	*S*-Mephenytoin	RU 42698	8.5	5.0 – 10.0	D4
CYP3A4	Midazolam	Ketoconazole	0.013	0.1 – 0.3	A6
CYP3A4	Midazolam	C-1073	9.3	~15	B3
CYP3A4	Midazolam	RU 42633	8.6	~10	C3
CYP3A4	Midazolam	RU 42698	8.7	~23	D5
CYP3A4	Testosterone	Ketoconazole	0.12	0.1	A7
CYP3A4	Testosterone	RU 42633	8.1	6.0 – 8.0	C4

Reference ID: 3072217

Reviewer's comments: The sponsor interpreted that most the inhibition mechanism seem to be competitive inhibition, however, definitive prediction of *in vivo* metabolism is very difficult with the results obtained from this *in vitro* study since none of the experiments were conducted under the condition that all analytes (mifepristone and its 3 active metabolites) coexisted.
The inhibitory effect of mifepristone and its metabolites on isoforms seem to have stronger than the sponsor claims. The given information should be interpreted with predicted concentration of mifepristone and its metabolites following therapeutic doses of mifepristone ([I]/Ki). Given that, mifepristone and its metabolites seem to be strong inhibitors for CYP3A3, and CYP2C8/9 and moderate inhibitor for CYP2A6. The sponsor used tranylcypromine as a control inhibitor for both CYP2A6 and CYP2B6 in Study C-1073-004. However, it is only acceptable for CYP2A6 but not for CYP2B6 since it is not selective inhibitor for CYP2B6.

Study C-1073-PK-006: In Vitro Interaction Studies of Mifepristone (RU 486) with Human MDR1 (P-gp), MRP1, MRP2, MRP3, BCRP, Transporters, and with Human OATP1B1, OATP1B3, OATP2B1, OCT1, OAT1, and NTCP Uptake Transporters

Mifepristone has been known to inhibit P-gp and used to block P-gp function and thus to restore sensitivity to cytotoxic drugs such as puromycin or doxorubicin. Mifepristone effectively interacted with the human MDR1, BCRP, and BSEP transporters in the vesicular transport assays. No effect was observed in the negative control experiments. According to these results, mifepristone is a potent inhibitor (substrate or inhibitor), with IC_{50} values in the low micromolar range.

Mifepristone also interacted with all the investigated uptake transporters. The potent inhibition was observed in the cases of OATP1B3, OATP1B1, and OATP2B1 with IC_{50} in the low micromolar range (< 10 μM). Inhibitory effects were less potent in case of NTCP and OCT1 and a slight decrease in reporter substrate transport was observed for the OAT1 transporter.

Reference ID: 3072217

TA	VT Assay	Summary
Mifepristone (RU 486)	MDR1	Mifepristone effectively inhibited the transport of the reporter substrate, NMQ mediated by MDR1 with an IC_{50} value of 1.8 μM and with an efficacy of 100%.
	MRP1	No interaction was detected.
	MRP2	No interaction was detected.
	MRP3	No interaction was detected.
	BCRP-HAM	Mifepristone effectively inhibited the estrone-3-sulfate transport by BCRP with an IC_{50} of 5.6 μM and with an efficacy of 87%.
	BSEP	Mifepristone effectively inhibited the taurocholate transport by BCRP with an IC_{50} of around 3 μM and with an efficacy of around 100%.
	K-CTRL	No interaction was detected.
	defMRP-CTRL	No interaction was detected.
	defBCRP-HAM-CTRL	No interaction was detected.
	Beta-gal-CTRL	No interaction was detected.

Study C-1073-PK-008: BCS Classification of Test Article Mifepristone: Preliminary Caco-2 Permeability Study

Note: There is discrepancy between the section 1.2 Comprehensive Summary of Contents and the actual study title. (Summary of Contents indicated the Study C-1073-PK-008 as a study titled "Determination of the Inhibition Potential (Ki) of C-1073, RU 42633, RU 42698, and RU 42848 Using Hyman Liver Microsome" but the actual title appearing in the report is shown above)

Objective: To determine the bi-directional permeability of mifepristone using Caco-2 cell monolayers

The apparent permeability of mifepristone was compared to those of pindolol and atenolol that are used as positive controls.

Results:

As shown in Table 43, the mifepristone Papp value was greater than the Papp of pindolol. Since pindolol is 90% absorbed in humans, mifepristone is expected to be well absorbed in humans, also. The B-to-A vs. A-to-B Papp ratio of mifepristone is listed in Table 44. The ratio is 1.79.

Table 43. Caco-2 permeability and recovery

Reference ID: 3072217

Compound	P_{app} (A-to-B) Mean ± SD (10^{-6} cm/s)	Recovery (%)
Mifepristone	28.9 ± 1.28	61.6 ± 0.466
Pindolol	19.4 ± 0.415	103 ± 0.198
Atenolol	0.391 ± 0.0412	93.4 ± 2.00

Table 44. Mifepristone B-to-A vs. A-to-B apparent permeability ratio

P_{app} Mean ± SD (10^{-6} cm/s)		Ratio (B-to-A) / (A-to-B)
A-to-B	B-to-A	
28.9 ± 1.28	51.6 ± 3.23	1.79

Reviewer's comments: This is non-GLP, preliminary study to determine the bi-directional permeability of mifepristone using Caco-2 cell monolayer. The sponsor's claim that mifepristone could be categorized into Class 2 of BCS is not acceptable.

4.2 Cover Sheet and OCP Filing

Reference ID: 3072217

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	202107	Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	mifepristone
Medical Division	DMEP	Drug Class	Glucocorticoid receptor antagonist
OCP Reviewer	Jee Eun Lee, Ph.D.	Indication(s)	Cushing's disease
OCP Pharmacometrics Reviewer		Dosage Form	tablet
OCP Team Leader	Jayabharathi Vaidyanathan, Ph.D.	Dosing Regimen	300 mg qd initial and titrated up to a maximum dose of 1200 mg (>60 kg)
Date of Submission	4/18/2011	Route of Administration	oral
Estimated Due Date of OCP Review	1/14/2012	Sponsor	Corcept Therapeutics
PDUFA Due Date	2/18/2012	Priority Classification	S
Division Due Date			

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	24		Bioanalytical study reports (22) and validation reports (2)
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2*		C-1073-05 PK in hepatic impairment and healthy, C-1073-19 PK in renal impairment and healthy
multiple dose:	X	2*		C-1073-05 PK study in hepatic impairment and healthy, C-1073-19 PK study in renal impairment and healthy

Reference ID: 3072217

Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	2		Food effect study with 600 mg and 1200 mg
fasting / non-fasting multiple dose:	X	1		Food effect study with 1200 mg/day
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	5		Studies with substrates of CYP2C9, CYP3A4, P-glycoprotein, and, a mild inhibitor of CYP3A4.
In-viitro effects of primary drug:	X	4		
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1		
hepatic impairment:	X	1		
PD:				
Phase 1:	X	1		
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		Three formulations were tested
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:		3		Food effect studies with high fat diet (2), with standard breakfast (1)
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				

BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		17		

Filability		
	"X" if yes	Comments
Application filable?	X	Comments to the Sponsor: Based on study reports for study C-1073-400 and study C-1074-415 it is noted that mifepristone plasma levels were analyzed in patients. Provide the pharmacokinetic datasets from these studies in SAS transport format. Also include data that was used for covariate analysis (e.g., co-medication of ketoconazole). If you have submitted the datasets, provide its location.
Submission in Brief: See the details below.	Reviewer's Comments (to the project manager): Please send the comments to the sponsor.	

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/s/

JEE E LEE
01/13/2012

JAYABHARATHI VAIDYANATHAN
01/13/2012

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	202107	Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	mifepristone
Medical Division	DMEP	Drug Class	Glucocorticoid receptor antagonist
OCP Reviewer	Jee Eun Lee, Ph.D.	Indication(s)	Cushing's disease
OCP Pharmacometrics Reviewer		Dosage Form	tablet
OCP Team Leader	Jayabharathi Vaidyanathan, Ph.D.	Dosing Regimen	300 mg qd initial and titrated up to a maximum dose of 1200 mg (>60 kg)
Date of Submission	4/18/2011	Route of Administration	oral
Estimated Due Date of OCP Review	1/14/2012	Sponsor	Corcept Therapeutics
PDUFA Due Date	2/18/2012	Priority Classification	S
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	24		Bioanalytical study reports (22) and validation reports (2)
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2*		C-1073-05 PK in hepatic impairment and healthy, C-1073-19 PK in renal impairment and healthy
multiple dose:	X	2*		C-1073-05 PK study in hepatic impairment and healthy, C-1073-19 PK study in renal impairment and healthy
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				

Reference ID: 2962451

fasting / non-fasting single dose:	X	2		Food effect study with 600 mg and 1200 mg
fasting / non-fasting multiple dose:	X	1		Food effect study with 1200 mg/day
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	5		Studies with substrates of CYP2C9, CYP3A4, P-glycoprotein, and, a mild inhibitor of CYP3A4.
In-viitro effects of primary drug:	X	4		
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1		
hepatic impairment:	X	1		
PD:				
Phase 1:	X	1		
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		Three formulations were tested
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:		3		Food effect studies with high fat diet (2), with standard breakfast (1)
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		17		

Reference ID: 2962451

Filability		
	"X" if yes	**Comments**
Application filable?	**X**	**Comments to the Sponsor: Based on study reports for study C-1073-400 and study C-1074-415 it is noted that mifepristone plasma levels were analyzed in patients. Provide the pharmacokinetic datasets from these studies in SAS transport format. Also include data that was used for covariate analysis (e.g., co-medication of ketoconazole). If you have submitted the datasets, provide its location.**
Submission in Brief: See the details below.	**Reviewer's Comments (to the project manager):** **Please send the comments to the sponsor.**	

* Studies are overlapped

Relevant submissions: NDA 20687 (Mifeprex), [redacted] (b) (4); IND 76480 ([redacted] (b) (4)

- Approved product: Mifeprex® tablet (200 mg strength) for the termination of pregnancy (through 49 days' pregnancy) in conjunction with misoprostol.
- Recommended dose for the termination of pregnancy: 600 mg once

Regulatory History for the Submission: 505(b)(2)

During the pre-NDA meeting on September 4, 2010, recommendations from clinical pharmacology were made to the sponsor, which include:

- DDI studies as guidance recommends including with a strong inhibitor of CYP3A4
- PK sampling in the Phase 3 trial was recommended for covariate analysis
- Evaluation of hepatic impairment at all stages was recommended

The sponsor did not conduct any additional DDI studies, however, it addressed that the information of the effect of ketoconazole (400 mg TID) was extracted from Phase 3 data as concomitant drug analysis.

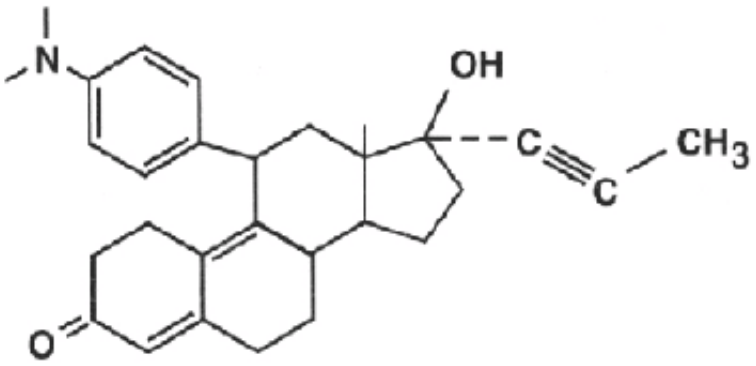
Background

Chemical formula: $C_{29}H_{35}NO_2$

Mifespristone is a substituted 19-nor steroid compound chemically designated as 11β-[p-(dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one.

Structural formula:

Reference ID: 2962451



Summary of the Submission:

The efficacy trial of [redacted] (b) (4) for the treatment of Cushing's syndrome (C1073-400) was conducted in 50 patients with Cushing's syndrome. The efficacy of mifepristone in Cushing's syndrome is also supported by literature. The safety of mifepristone is supported from the study C1073-400 and the long-term extension study, C1073-415. Additional safety data from Corcept-sponsored studies conducted in other indications as well as from its clinical pharmacology program were provided. A total of 51 cases, 44 out of them were treated with therapeutic courses of mifepristone for up to 24 months with doses ranged from 200 to 2000 mg/day (~5 to 30 mg/kg/day)

C1073-400 study

- 24-week, open-label study in patients with Cushing's syndrome
- 50 subjects were assigned
- Dose:
  - 300 mg QD
  - Optimal dose is not known, dose escalation was undertaken with clinical observation
  - After 14 days of dosing at 300 mg QD, dose escalations in 300-mg increments could be made every four weeks if no clinical improvement observed but well-tolerated
  - Maximum dose 1200 mg QD (or 900 mg QD for subjects weighing < 60 kg)

Total of 13 Clinical Pharmacology studies are included (See Appendix)

- The to-be-marked formulation was used in the Phase 3 study
- Bioavailability across three different formulations was reported to be similar.
- Food effect was observed which increases as dose increases (fed/fasted exposure ratio: 1.29 following single dose of 600 mg, 1.42 following single dose of 1200 mg)

Reference ID: 2962451

- Hepatic/renal impairment did not change drug exposure significantly. No dose adjustment is proposed by the sponsor.
- The upper bound of CI for QTc prolongation following 1800 mg multiple dose was 14 and 15 ms after 6 and 16 hours on Day 14.

Total of 5 Biopharmaceutics studies are included

- PK-C-1073-002: In vitro evaluation of the binding of mifepristone and three metabolites to human plasma proteins
- PK-C1073-003/PK-C1073-004/ PK-C1073-008: In vitro studies for inhibition potential of various CYP enzymes in microsomes
- PK-C1073-006: In vitro study for potential DDI with transporters

PK Characteristics of mifepristone

- Bioavailability for 20 mg: 69%
- Fraction eliminated in bile (fb):~90%
- Fraction excreted in urine<10%
- Protein binding:
  - ~99.2% for mifepristone, 96.1~98.9% for metabolites
- CYP3A4 mediated metabolism
  - 3 Active metabolites
  - RU 42633, RU 42848 (demethylation)
  - RU 42698 (hydroxylation)

Recommendation: The submission is filable from a Clinical Pharmacology perspective.

Reference ID: 2962451

Appendix 1: Summary of Clinical Pharmacology Studies

Study Number	Study Type	Dose	Population	Number of Subjects	
C-1073-05	Hepatic impairment	600 mg × 1, followed 2 weeks later by 600 mg/day for 7 days	Healthy and patients with hepatic impairment	10 impaired, 10 healthy	Phase I study of the pharmacokinetics of single and multiple doses of C-1073 (mifeprisone) in hepatic impairment as compared to healthy volunteers
C-1073-12	Food effect	600 mg single dose	Healthy volunteers	50	Phase I, open-label, crossover study of the pharmacokinetics and safety of single doses of orally adminis mifeprisone in fed versus fasting state in healthy volunteers
C-1073-16	DDI, CYP2C8/9 substrate (fluvastatin)	1200 mg/day for 7 days	Healthy volunteers	20	Phase I, open-label, fixed-sequence study to determined the effect of single and multiple oral doses of (b) (4) on the pharmacokinetics of a single oral dose of fluvastatin (a CYP2C9 probe) in healthy volun
C-1073-19	Renal impairment	1200 mg/day for 7 days	Healthy and patients with renal impairment	10 impaired, 8 healthy	Phase I, open=-label, adaptive two-stage study of the effects of renal impairment on the pharmacokinetic mifepristone and its active metabolites following multiple doses of mifepristone in volunteers with impai and normal renal function – Stage 1
C-1073-20	Food and dose effects	1200 mg single dose (fed/fasted) and 300, 600, or 1200 mg single dose (fasted)	Healthy volunteers	24	Phase I, randomized, open-label study to determine the effect of food and the effect of dose on the pharmacokinetics of a single dose of (b) (4) in healthy volunteers
C-1073-22	Bioavailability, formulation change	300 mg	Healthy volunteers	15	Phase I, open-label, randomized three-way crossover study of the effects of formulation and dissolution r on the pharmacokinetics of mifeprisone following a single 300 mg dose of mifeprisone in healthy volunt
C-1073-23	DDI, P-gp substrate (digoxin)	1200 mg/day for 10 days	Healthy volunteers	22	Phase I, open-label, fixed-sequence, three-treatment study to determined the effect of single and multiple doses of mifepristone on the pharmacokinetics of digoxin at steady state
C-1073-24	DDI, CYP3A substrate (alprazolam)	1200 mg × 1 then 1200 mg/day for 12 days	Healthy volunteers	16	Phase I, open-label, fixed-sequence, three-period crossover study to determined the effects of single and multiple doses of mifepristone on the pharmacokinetics of a single dose of alprazolam in healthy volunte
C-1073-25	DDI, CYP3A substrate (simvastatin)	1200 mg/day for 10 days	Healthy volunteers	20	Phase I, open-label, fixed-sequence, two-period, three treatment crossover study to determined the effect single and multiple doses of (b) (4) on the pharmacokinetics of a single dose of simvastatin in healthy volunteers
C-1073-26	DDI, CYP3A inhibitor (cimetidine)	300 mg/day for 14 days	Healthy volunteers	20	Phase I, open-label, fixed sequence, three-period, six-treatment crossover study to determine the effects o single and multiple oral doses of cimetidine and (b) (4) on the pharmacokinetics of mifepristone and th urinary excretion of cimetidine in healthy volunteers

Reference ID: 2962451

C-1073-27	Food effect, multiple dose	1200 mg/day for 7 days (fasting) and 8 days (fed)	Healthy volunteers	24	Phase I, open-label, randomized, crossover study to determined the effects of a typical meal (34% fat) as compared to fasting on the pharmacokinetics of mifepristone and its metabolites following single and mu daily oral doses of Corlux in healthy volunteers
C-1073-300	TQT	600 or 1800 mg/day for 14 days	Healthy volunteers	105	Thorough ECG trial comparing Corlux and placebo
C-1073-425	Biomarker, HDL impact	600 mg/day for 6 weeks	Healthy volunteers	20	Placebo-controlled two-period study to determine the effects of multiple doses of Corlux on the high den lipoprotein (HDL-C) levels in healthy volunteers

Reference ID: 2962451

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/s/

JEE E LEE
06/17/2011

JAYABHARATHI VAIDYANATHAN
06/17/2011

BIOPHARMACEUTICS FILING REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202-107	**Reviewer:** Minerva Hughes, Ph.D.	
Submission Date:	15 April 2011		
Division:	Division of Metabolism and Endocrinology Products	**Team Lead:** Angelica Dorantes, Ph.D.	
Sponsor:	Corcept Therapeutics	**Supervisor:** Patrick Marroum, Ph.D.	
Trade Name:	(b) (4)	**Date Assigned:**	20 April 2011
Generic Name:	Mifepristone tablets	**Date of Review:**	14 June 2011
Indication:	Hypercortisolism in patients with Cushing's syndrome	**Type of Submission:** Original NDA 505(b)(2)	
Formulation/strengths	Tablet/ 300 mg		
Route of Administration	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 demonstrates pH-dependent solubility with the greatest solubility achieved in acidic media (~ 25 mg/mL at pH 1.5). Solubility declines rapidly as the pH is increased, and at pH values above 2.5, the solubility of mifepristone is less than 1 mg/mL. Reference was made to DMF (b) (4) for drug substance chemistry, manufacturing and controls.

The drug product is formulated as 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 a (b) (4) process. The following method is proposed for control of the critical drug release/performance characteristics.

- USP Apparatus 2; 50 mM Citrate buffer, pH 2.20, 900 mL
- 50 rpm paddle speed
- Sampling at 10, 30, 45, 60, and 75 minutes
- Quantitative analysis by using HPLC/UV detector
- Limit: *Two-point specification*
  - 10 minutes: (b) (4)
  - 60 minutes: Q (b) (4)

Given the solubility and release characteristics, dissolution is a critical factor affecting drug absorption and thus, efficacy and safety performance.

BIOPHARMACEUTIC INFORMATION: In support of approval, NDA 202-133 includes the following biopharmaceutics data for review and evaluation:

- **Drug substance solubility data:** Graphed data were submitted. A complete solubility study report, including numerical data at all pH sampling points should be submitted to fully understand the solubility characteristics of the molecule and the impact of pH changes on dissolution performance.
- **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. (*note: this study will be reviewed by Biopharmaceutics to evaluate the adequacy of the proposed method and specification for assuring acceptable product performance; however, final study conclusions are deferred to the Clinical*

Reference ID: 2960230

Pharmacology Reviewer)

- **Dissolution Method Validation Report No. 10.6404.00:** Method validation report evaluating validation parameters such as system suitability, accuracy, precision, specificity, linearity, limit of quantitation, range and robustness of the proposed dissolution method and HPLC analysis system. This report does not address method development and discriminating power.
- **Batch analyses data:** Batch analyses data were submitted for clinical lots and three primary stability batches. Different dissolution methods were used throughout the clinical development program. Therefore, the adequacy of bridging and batch-to-batch comparability will need to be reviewed closely.
- **Drug product stability data:** Long-term stability data through 24 months for supportive drug product lots and 9 months for registration lots were submitted in the initial NDA. Accelerated data through 6 months were also submitted.

A pre-NDA meeting was held with the applicant on 14 September 2010 (refer to FDA meeting minutes of 26 Oct 2010). The applicant was advised that the NDA should include a dissolution method development report outlining the selection criteria used to determine the optimal equipment, media, agitation speed, pH, assay, etc. Testing on at least twelve samples per testing variable, and dissolution/release data (individual, mean, SD, profiles) reported as the cumulative percentage of drug eluted with time were requested. In addition, studies performed to evaluate the discriminating capabilities of the method and validation data were requested. A dissolution method validation report and a description of the claimed optimal method conditions were submitted, but a complete method development report was not located.

RECOMMENDATION:

From a biopharmaceutics perspective, NDA 202-107 for (b) (4) (mifepristone) Tablets is **fileable.**

However, the following information request should be conveyed to the Applicant.

We acknowledge that you provided the dissolution method validation report that was requested during the pre-NDA meeting held on 26 October 2010. However, please note that the dissolution method validation report that you provided includes the validation of the analytical method and the quality testing of the dissolution methodology (i.e., robustness, etc.), but it does not include the dissolution information collected during the development of the proposed dissolution test and how you reached to the conclusion that this test is the most optimal method for the evaluation of your product. Therefore, to support your application, please provide the dissolution method development report outlining the experiments performed and providing the entire data collected (b) (4) to support revising the (b) (4) dissolution method. The report should clearly outline the following information.

- Complete mifepristone pH solubility over the pH range of 1 to 7.5 (both numerical and graphed data), including a description of the buffers and conditions used to determine equilibrium solubility. Solution pH data measured before and after the product should be summarized.
- The developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. Testing conditions used for each test and complete dissolution profile data (individual, mean, SD, profiles) should be clearly stated.
- Testing conducted to demonstrate the discriminating capability of the proposed method to manufacturing changes.

Minerva Hughes
Biopharmaceutics Reviewer, ONDQA

Patrick Marroum
Biopharmaceutics Supervisor, ONDQA

cc: filed in DARRTS

Reference ID: 2960230

APPEARS THIS WAY ON ORIGINAL

Reference ID: 2960230

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/s/

MINERVA HUGHES
06/14/2011

PATRICK J MARROUM
06/14/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202107Orig1s000

PHARMACOLOGY REVIEW(S)