CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020973

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

AUG 19 1999

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-973

Trade Name: Aciphex® Tablets

Active Ingredient: Rabeprazole Sodium

Sponsor: Eisai, Inc.

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Submission Date: 3/3/1999

Stamp Date: 3/16/1999

Review Date: 5/25/1999

Draft Date: 8/19/1999

Final Review Date: 8/19/1999

Type of Submission: Memorandum Regarding Dissolution Testing of Aciphex Tablets

Synopsis:

Rabeproazole is a substituted benzimidazole proton-pump inhibitor. Proposed indications include healing and long-term maintenance of healing of gastroesophageal reflux disease (GERD), healing of duodenal ulcers, and treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome. The recommended dose is 20 mg orally, once a day, for up to 4-8 weeks, for all indications with the exception of pathological hypersecretory conditions, where the recommended starting dose is 60 mg once a day.

NDA 20-973 for Aciphex (rabeprazole sodium) enteric-coated tablets was submitted to the Agency on Mar 31, 1998. On Jan 29, 1999, the Agency found the submissions for Aciphex 20 mg enteric coated tablets approvable provided the Firm addresses several issues. In their response, the Firm adequately addressed Agency concerns. However, the Agency had requested the Firm collect data from the acid resistant stage of the dissolution testing procedure (see attachment). The Firm is currently collecting data according to Agency recommendation for dissolution methods and specification and will submit the data as soon as possible.

NDA 20-973 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II) and is found to be approvable.

/S/ 8/19/99

Suliman I. Al-Fayoumi, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by David Lee, Ph.D., Team leader 8/19/1999

FT initialed by David Lee, Ph.D., Team leader /S/ 8/19/99

cc: HFD-180: NDA 20,973 (1x); DIV FILE (1x); MWALSH (1x); DLEE (1x); SALFAYOUMI (1x); HFD-870 JHUNT (1x); MCHEN (1x); HFD-850 SHUANG (1x); CDR: ATTN Barbara Murphy

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-973

Trade Name: Aciphex® Tablets

Active Ingredient: Rabeprazole Sodium

Sponsor: Eisai, Inc.

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Response to Action Letter

Submission Date: 3/3/1999

Stamp Date: 3/16/1999

Review Date: 5/25/1999

Draft Date: 8/2/1999

Final Review Date: 8/4/1999

Synopsis:

Rabeproazole is a substituted benzimidazole proton-pump inhibitor. Proposed indications include healing and long-term maintenance of healing of gastroesophageal reflux disease (GERD), healing of duodenal ulcers, and treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome. The recommended dose is 20 mg orally, once a day, for up to 4-8 weeks, for all indications with the exception of pathological hypersecretory conditions, where the recommended starting dose is 60 mg once a day.

NDA 20-973 for Aciphex (rabeprazole sodium) enteric-coated tablets was submitted to the Agency on Mar 31, 1998. On Jan 29, 1999, the Agency found the submissions for Aciphex 20 mg enteric coated tablets approvable provided the Firm addresses several issues (see attachments). This submission represents the Firm's response to the FDA action letter.

Reviewer's Comments

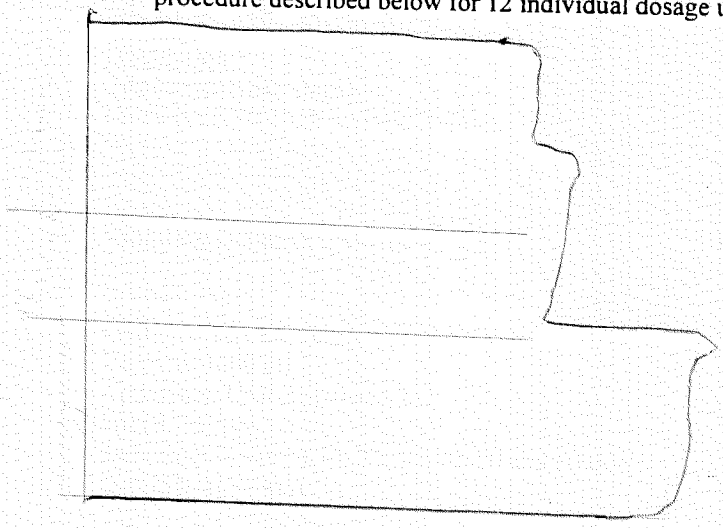
1. Preliminary analysis of the $AUC_{(0-\infty)}$ data indicated that mean ± SD values for $AUC_{(0-\infty)}$ in males was 745 ± 325 (Median = 652) and in females was 1047 ± 546 (Median = 914). The FDA requested a reanalysis of the data from the gender analysis using valid $AUC_{(0-\infty)}$ data from study #A001-114 for a potential gender effect. Upon reanalysis, the Firm suggests that the difference in mean $AUC_{(0-\infty)}$ values between genders is not related to gender ($p>0.05$), but rather correlates to differences in body weight-related variables, such as height and lean body mass (Table 1). Thus, the Firm concludes that administering a fixed 20 mg rabeprazole dose to a cohort of physically smaller individuals produces greater $AUC_{(0-\infty)}$ due primarily to the fact that they received higher mg/kg doses.
There was a safety concern stemming from the observation of up to 50% higher rabeprazole plasma levels in females compared to males. However, Dr. Gallo-Torres (medical officer) did point out the wide safety margin for rabeprazole that was noted in clinical trials. In addition, no dosage adjustment was required for patients with mild to moderate hepatic dysfunction who had up to two fold higher rabeprazole plasma levels in a single dose study and up to 20% higher levels in a multiple dose study compared to healthy individuals. Hence, it is unlikely that a 50% increase in rabeprazole plasma levels would lead to any toxicity. The response provided by the Firm regarding potential gender effect on $AUC_{(0-\infty)}$ is found to be acceptable by the Agency.

Table 1. Correlation Analysis of $AUC_{(0-\infty)}$ Values for Covariables

Covariable	Pearson Correlation Coefficient (R)	P-Value
Age	0.181	0.366
Body Weight	-0.223	0.264
Height	-0.366	0.0602
Lean Body Mass	-0.347	0.0757
Body Mass Index (BMI)	0.0172	0.932

2. Upon reviewing data from study #A001-101 (warfarin-rabeprazole *in vivo* drug-drug interaction study), it was noted that there was a large (70%), though statistically insignificant, increase in AUC values for R-warfarin. The Agency commented that the length of time between the single doses of warfarin administered in the study appeared to be insufficient for complete washout of warfarin. In response, The Firm submitted data for all enrolled subjects and suggested the 70% increase in R-warfarin AUC was due to one extreme outlier (subject 120). Removing this outlier's data from the analysis indicates no difference in R-warfarin pharmacokinetics before and after rabeprazole. Upon review of study conduct and analytical procedures, no anomalous events were found to explain this finding. Furthermore, the Agency requested demographic information on all the subjects in study #E3810-8001-101 and the Firm provided the required data in tabular form (see attachments). Upon review, the Agency found no major demographic differences between subject 120 and the other enrolled subjects. Hence, **the response provided by the Firm regarding a potential drug-drug interaction effect on $AUC_{(0-\infty)}$ is found to be acceptable by the Agency.**

3. The Agency requested the Firm submit data from the acid resistance stage of the dissolution testing procedure described below for 12 individual dosage units of rabeprazole.



The Firm is currently collecting data according to the Agency recommendation for dissolution method and specification and will submit the data as soon as possible.

Recommendations:

The Firm's response to questions by the Agency regarding NDA 20-973 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II) and is found to be acceptable provided the Firm submits dissolution data for rabeprazole in the acid resistance stage to the satisfaction of the Agency.

/S/ 8/4/99

Suliman I. Al-Fayoumi, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by David Lee, Ph.D., Team leader /S/

FT initialed by David Lee, Ph.D., Team leader 8/2/1999, 8/4/1999 /S/ 8/4/99

cc: HFD-180: NDA 20,973 (1x); DIV FILE (1x); MWALSH (1x); DLEE (1x); SALFAYOUMI (1x); HFD-870 JHUNT (1x); MCHEN (1x); HFD-850 SHUANG (1x); CDR: ATTN Barbara Murphy

AUG 4 1999

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-973

Trade Name: Aciphex® Tablets

Active Ingredient: Rabeprazole Sodium

Sponsor: Eisai, Inc.

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Labeling Revision

Submission Date: 3/3/1999

Stamp Date: 3/16/1999

Review Date: 5/25/1999

Draft Date: 8/2/1999

Final Review Date: 8/4/1999

Synopsis:

Rabeproazole is a substituted benzimidazole proton-pump inhibitor. Proposed indications include healing and long-term maintenance of healing of gastroesophageal reflux disease (GERD), healing of [redacted] duodenal ulcers, and treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome. The recommended dose is 20 mg orally, once a day, for up to 4-8 weeks, for all indications with the exception of pathological hypersecretory conditions, where the recommended starting dose is 60 mg once a day.

NDA 20-973 for Aciphex (rabeprazole sodium) enteric coated tablets was submitted to the Agency on Mar 31, 1998. On Jan 29, 1999, the Agency found the submissions for Aciphex 20 mg enteric coated tablets to be approvable provided the Firm addresses several issues (see attachments). On Mar 5, 1999, the Firm submitted a response to the FDA action letter, which included the package insert incorporating all the requested changes. This submission represents the draft labeling submitted by the Firm as the annotated, marked-up revised version. For purpose of this review, this current review will only address clinical pharmacology- related issues.

Proposed Labeling Changes

[redacted]

4 Page(s) Redacted

DRAFT LABELING

[redacted]

Recommendations:

The amended supplemental NDA 20-973 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II) and is found to be approvable regarding issues related to **Clinical Pharmacology**. However, it should be noted that:

1) The reviewing medical officer should be consulted on the "Geriatric Use" issue under the "Precautions" section.

2) The following recommendations should be forwarded to the applicant, as appropriate:

[redacted]

/S/ 8/4/99

Suliman I. Al-Fayoumi, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by David Lee, Ph.D., Team leader 8/2/1999, 8/4/1999

FT initialed by David Lee, Ph.D., Team leader /S/ 8/4/99

cc: HFD-180: NDA 20,973 (1x); DIV FILE (1x); MWALSH (1x); DLEE (1x); SALFAYOUMI (1x); HFD-870 JHUNT (1x); MCHEN (1x); HFD-850 SHUANG (1x); CDR: ATTN Barbara Murphy

Clinical Pharmacology and Biopharmaceutics Review

DEC 21 1998

NDA 20-973

Rabeprazole sodium
20 mg enteric-coated tablets
Aciphex™
Eisai Inc.

Reviewer: Carol Cronenberger, Ph.D.
Type of Submission: Original NME (1S – 10 month review)
Submission Date: March 31, 1998

SYNOPSIS:

NDA 20-973 for Aciphex (rabeprazole sodium) enteric-coated tablets was submitted to the Agency on March 31, 1998. Rabeprazole is a substituted benzimidazole proton-pump inhibitor, which is structurally similar to omeprazole and lansoprazole. Proposed indications are healing and long-term maintenance of healing of gastroesophageal reflux disease (GERD), healing of [redacted] duodenal ulcers, and treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome. The recommended dose is 20 mg orally, once a day, for up to 4-8 weeks, for all indications with the exception of pathological hypersecretory conditions, where the recommended starting dose is 60 mg once a day. As rabeprazole is very unstable in acidic environment, the enteric-coated tablets are designed to be released and absorbed after leaving the stomach.

The sponsor has submitted 38 pharmacokinetic/bioavailability/pharmacodynamic studies to the NDA; 33 of these studies were reviewed in detail.

The sponsor has adequately addressed the following:

- Mass balance and metabolic profile for rabeprazole after oral administration,
- In vitro studies addressing the biotransformation pathways for rabeprazole,
- Dose-proportionality of rabeprazole after single and multiple oral doses of 10 mg to 40 mg,
- Pharmacokinetics for rabeprazole and its metabolites after single and multiple oral doses,
- Absolute bioavailability of rabeprazole after oral administration,
- Data for the pharmacokinetics of rabeprazole in patients with renal failure,
- Preliminary data for patients with hepatic impairment,
- Pharmacokinetics for rabeprazole in healthy, elderly subjects,
- Drug interaction studies between rabeprazole and antacid, theophylline, diazepam, ketoconazole, and digoxin,
- Pharmacodynamics of rabeprazole after single and multiple doses of 10 mg to 40 mg,
- Preliminary pharmacokinetic/pharmacodynamic relationships,
- Dissolution method and specification.

Equivalence between the 20 mg to-be-marketed formulation (i.e., a full-scale batch made at the proposed manufacturing site) and a 20 mg clinical batch was established according to the Two One-Sided Tests Procedure for the 90% confidence interval range of 80-125% using log-transformed data for AUC_{0-T} and $AUC_{0-\infty}$, however, the equivalence criteria were not met for Cmax. Based upon the mode of drug action and the duration of pharmacologic effect for rabeprazole, a concensus was reached between Medical Officers (Drs. John Senior and Hugo

Gallo-Torres) from the Division of Gastrointestinal and Coagulation Drug Products and members of OCPB, at the Clinical Pharmacology and Biopharmaceutics Briefing held December 18, 1998, that the differences observed for Cmax for the two studied tablets were not significant from a clinical perspective.

The effect of food on the bioavailability of rabeprazole and the protein-binding of rabeprazole were not adequately examined.

A cross-study comparison of the pharmacokinetics for rabeprazole in Japanese and American subjects was included. Although a study examining the influence of gender on the disposition of rabeprazole was not submitted, an analysis of the data from the pivotal bioequivalence study (#E3810-A001-114) was performed to compare differences in the pharmacokinetics of rabeprazole between males and females. However, this analysis was not performed using valid data for $AUC_{0-\infty}$.

Even though preliminary results were available with respect to the pharmacokinetics of rabeprazole in subjects with cirrhosis, the data were not analyzed in order to assess whether there were statistically significant differences between this population and healthy volunteers.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed Section 6 of NDA 20-973 for rabeprazole sodium (Aciphex). Although the sponsor has submitted studies which are consistent with the Agency's regulations as covered under 21 CFR 320, there are some issues which need to be addressed. Therefore, OCPB has the following recommendations:

1. Although equivalence was established between the to-be-marketed and clinical batches for AUC_{0-T} and $AUC_{0-\infty}$, Cmax values did not meet the criteria (90% CI: 68.5-102.6). Specifically, mean Cmax values for the to-be-marketed formulation [redacted] were approximately 5% lower than the mean Cmax values for the clinical formulation [redacted] However, based upon the mode of drug action and the duration of pharmacologic effect for rabeprazole, a concensus was reached between Medical Officers from the Division of Gastrointestinal and Coagulation Drug Products and members of OCPB at the CPB Briefing held December 18, 1998, that the differences observed for Cmax for the two studied tablets were not significant from a clinical perspective.

2. The sponsor is requested to perform a well-controlled and adequate study examining the effect of food on the bioavailability of rabeprazole according to the draft FDA "Guidance for Industry, Food-Effect Bioavailability and Bioequivalence Studies," October, 1997.

3. The sponsor is requested to perform a study to assess the in vitro protein-binding of RBP, covering the relevant concentration range.

4. Two studies (#A001-004 and #A001-108) assessed the pharmacokinetics of rabeprazole in patients with varying degrees of hepatic impairment, and demonstrated that there were some differences when compared to healthy subjects. The Medical Officer is requested to evaluate whether adjustments in rabeprazole administration are necessary for the hepatically impaired population.

5. The sponsor needs to reanalyze the data for the gender analysis using valid $AUC_{0-\infty}$ data from Study #A001-114 (submitted to the Agency on December 11, 1998).

6. The sponsor needs to submit data from the Acid Resistance stage of the dissolution testing procedure (see below) for 12 individual dosage units of rabeprazole.

The following dissolution method and specification are recommended:

[redacted]

The above Recommendation section, as well as the labeling comments found on page 48-51 of this review, should be sent to the sponsor as appropriate. Before initiating any of the outlined studies, the sponsor should submit each study protocol for review by OCPB staff.

Carol Cronenberger, Ph.D.
OCPB, Divison of Pharmaceutical Evaluation II

/S/ 12/24/98

FT initialed by John Hunt, Acting Team Leader
OCPB, Division of Pharmaceutical Evaluation II

/S/ 12/21/98

cc: NDA 20-973, HFD-180, HFD-850 (Lesko), HFD-870 (Chen, Hunt), Central Document Room (Barbara Murphy).

TABLE OF CONTENTS:

ABBREVIATIONS USED:

A – accuracy
A_{feces} – amount of radioactivity recovered in the feces
A_{urine} – amount of radioactivity recovered in the urine
A_{total} – total amount of radioactivity recovered
ACTH – adrenocorticotropic hormone
AE – adverse event
ALT – alanine transaminase
ANOVA – analysis of variance
AST – aspartate transaminase
AUC_{0-T} – area under the plasma concentration vs time curve from time=0 to a predetermined time after dosing
$AUC_{0-\infty}$ - area under the plasma concentration vs time curve from time=0 to time=infinity
AV – atrioventricular
BA – bioavailability
BE – bioequivalence
BW – body weight
C_{24h} – concentration of drug in the plasma at 24 hours post-dose
C_{pl} – concentration of drug in the plasma
C_{wb} – concentration of drug in the whole blood
Cmax – the maximum concentration of drug in the plasma over the sampling interval
Cmin – the minimum concentration of drug in the plasma over the sampling interval
Cl_{oral} – oral clearance
Cl_{renal} – renal clearance
Cl_T – total body clearance
Cl/F – oral clearance
CI – confidence interval
CRF – case report form
CV – coefficient of variation
CYP450 – cytochrome P450
DEA - diethylamine
DM – desmethyl rabeprazole
DMTE – desmethyl thioether rabeprazole
DU – duodenal ulcer
E3810- rabeprazole sodium
ECG - electrocardiogram
EM – extensive metabolizer
GE - gastroesophageal
GERD – gastroesophageal reflux disease
GLM – general linear model

HPLC – high performance liquid chromatography
IS – internal standard
kel – elimination-rate constant
$ki_{apparent}$ – apparent inhibitory constant
$km_{apparent}$ – apparent Michaelis constant
LDH – lactose dehydrogenase
LOQ – limit of quantification
LY307640 – rabeprazole sodium
MA – mercapturic acid

MeOH - methanol
MRT – mean residence time
ND – not determined
NDA – new drug application
NR - not reported
NSAID – non-steroidal anti-inflammatory drug
OMP – omeprazole
P – precision
PD – pharmacodynamic
PK – pharmacokinetic
PM – poor metabolizer
PPI – proton-pump inhibitor
PVC – premature ventricular contraction
QC – quality control
RBP – rabeprazole sodium
RIA – radioimmunoassay
S – rabeprazole sulfone
SAS – statistical analysis system
SC – standard (calibration) curve
SD – standard deviation
SGOT – serum glutamic-oxaloacetic transaminase
SGPT – serum glutamic-pyruvic transaminase
TE – rabeprazole thioether
TEC – rabeprazole thioether carboxylate
Tmax – the time of maximum plasma drug concentration
UM-1 – mercapturic acid
UM-2 – thioether carboxylate
UV – ultraviolet
Vd – volume of distribution
Vd_{ss} – volume of distribution at steady-state
$Vmax_{apparent}$ – apparent maximum velocity

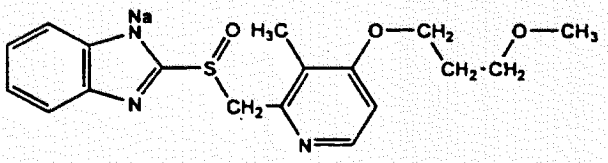
I. BACKGROUND:

Rabeprazole is a substituted benzimidazole proton-pump inhibitor which is structurally similar to the marketed compounds, ompeprazole and lansoprazole. The proton-pump inhibitors are metabolized to active sulphenamide derivatives which specifically inhibit H^+/K^+-ATPase activity on the surface of the gastric parietal cells, thus blocking the final step in gastric acid secretion. The PPIs have proven to be useful therapeutic agents in treating a variety of peptic acid-related disorders, including GERD, DU, GU, and pathological hypersecretory disorders. The clinical benefits include potential life-saving therapy, alleviation of suffering, and improving the quality of life for patients afflicted with these disorders.

The sponsor has submitted 38 BA/PK/PD studies in support of the clinical pharmacology and biopharmaceutics requirements for NDA 20-973. These studies were performed in Japan, Europe, and in the United States from 1988 to 1997. Five of these studies were not reviewed in depth, as they contained unreliable data or irrelevant information (see discussion under BA and PK Studies for details).

II. CHEMISTRY

Rabeprazole sodium is the active ingredient in rabeprazole sodium tablets (20 mg) and has the molecular formula $C_{18}H_{20}N_3NaO_3S$. The chemical structure of RBP is shown below.



RBP exists as an enantiomer and is supplied in formulation as a racemate. It is a white to slightly yellowish white solid with a molecular weight of 381.43 gm. RBP is practically insoluble in non-polar solvents, such as toluene and hexane, but is very soluble in water, methanol, dichloromethane, acetone, and ethyl acetate. Manufacturing at full scale has always produced an

III. FORMULATION

Drug product used in the clinical development program was manufactured at Eisai Company, Ltd. The proposed site of manufacture for commercial-scale production is The proposed commercial scale of manufacture will be approximately

Tablet strengths of 1 mg, 5 mg, 10 mg, and 20 mg RBP were used in the PK studies. The pivotal clinical trials employed RBP doses of 10 mg and 20 mg. During drug product development, the formulation underwent several changes, including addition of carnauba wax, different quantities of undercoating excipients, and deletion of specific ingredients. Table 1 in Appendix I displays the formulations of all tablet strengths used in the clinical trials and PK studies. The three 20 mg formulations were identical, with the exception of a trace quantity of ink added to the to-be-marketed product for imprinting. There were five different formulations evaluated for the 10 mg RBP tablets. The sponsor had originally planned to market both a 10 mg and a 20 mg RBP tablet, however, subsequently withdrew the NDA submission for the 10 mg tablet strength on December 4, 1998. Table III.1. lists the ingredients and their function for the to-be-marketed 20 mg RBP tablets.

Table III.1. Formulation for the to-be-marketed 20 mg RBP tablet.

Ingredient	
Rabeprazole sodium	
Mannitol	
Magnesium oxide	
Low-substituted hydroxypropyl cellulose	
Hydroxypropyl cellulose	
Magnesium stearate	
Ethylcellulose	
Hydroxypropyl methylcellulose Phthalate	
Diacetylated monoglycerides	
Talc	
Titanium dioxide	
Ferric oxide (yellow)	
Carnauba Wax	

IV. BIOEQUIVALENCE STUDIES

There were five BE studies included in this NDA, the purpose of which was to link some of the formulations of RBP used in the different studies throughout the drug development process. Each study is briefly discussed below.

A. Study #J081-009

This was a randomized, two-treatment, two-period, two-way crossover study in 24 healthy, Japanese, male volunteers to evaluate the BE of 2x10 mg vs 1x20 mg RBP tablets. As observed in the table below, the results indicate that the two treatments were not BE according to the Two One-Sided Tests Procedure and 90% CI range of 80-125% using log-transformed data for AUC_{0-24} and Cmax.

Table IV.1. Mean±SD (%CV) PK parameters and results of BE analysis.

	2x10 mg RBP (N=24)	1x20 mg RBP (N=24)	Geometric Mean Ratio (%) (2x10mg/1x20mg)	90% CI for log-transformed data
AUC_{0-24} (ng*hr/ml)	1203±707 (59%)	1111±714 (64%)	101.9	78.0;98.8
Cmax (ng/ml)	579±218 (38%)	593±283 (48%)	100.6	78.4;117.9
Tmax (hr)	3.3±0.9 (27%)	3.5±1.0 (29%)	-	-

B. Study #J081-010

This was a randomized, two-treatment, two-period, two-way crossover study in 24 healthy, Japanese, male volunteers to evaluate the BE of 2x5 mg vs 1x10 mg RBP tablets. As observed in the table below, the results indicate that the two treatments were not bioequivalent according to the Two One-Sided Tests Procedure and 90% CI range of 80-125% using log-transformed data for Cmax.

Table IV.2. Mean±SD (%CV) PK parameters and results of BE analysis.

	2x5 mg RBP (N=24)	1x10 mg RBP (N=24)	Geometric Mean Ratio (%) (1x10mg/2x5mg)	90% CI log-transformed data
AUC_{0-24} (ng*hr/ml)	512±274 (54%)	521±240 (46%)	100.7	88.0;103.8
Cmax (ng/ml)	276±124 (45%)	289±105 (36%)	101.6	78.1;107.2
Tmax (hr)	3.9±1.3 (33%)	3.5±1.2 (34%)	-	-

C. Study #A001-109

This was a randomized, two-treatment, two-period, two-way crossover study in 24 healthy, American, male and female volunteers to evaluate the BE of 2x10 mg vs 1x20 mg RBP tablets. As observed in the table below, the results indicate that the two treatments were BE according to the Two One-Sided Tests Procedure and 90% CI range of 80-125% using log-transformed data for the AUC values and for Cmax. It should be noted that one subject was excluded from the data analysis as he was considered to be an outlier. The two treatments were not BE based on Cmax (CI - 95.2;129.3) when this subject was included in the data analysis. The results are presented in Table IV.3. below.

Table IV.3. Mean±SD (%CV) PK parameters and BE results excluding Subject 907.

	RBP 2x10 mg (N=22)	RBP 1x20 mg (N=22)	Geometric Mean Ratio (%) (2x10 mg/1x20 mg)	90% CI Log-Transformed Data
AUC_{0-24} (ng*hr/ml)	885.5±443.9 (50%)	877.8±569.9 (65%)	Ratio=105.56	(95.35;116.86)
$AUC_{0-\infty}$ (ng*hr/ml)	899.3±446.8 (50%)	893.2±572.4 (64%)	Ratio=105.13	(95.28;116.00)
Cmax (ng/ml)	603.0±241.6 (40%)	587.0±300.8 (51%)	Ratio=105.43	(92.11;120.67)