20 mg, and 40 mg) compared to placebo, on 24-hour intragastric acidity and plasma gastrin levels following a 7-day treatment period.

Intragastric Acidity

At each hour for a 24-hour period after the last dose, the mean intragastric pH was higher after 7 days of treatment with 10, 20, or 40 mg RBP, than after 7 days of treatment with placebo. Table VIII.8. provides the mean±SD and median intragastric acidity data for each AUC interval during the different treatments. At all time intervals for AUC on Day 7, the intragastric acidity was statistically significantly lower for all doses of RBP compared to placebo ($p<0.001$), indicating a significant effect of RBP on gastric acidity at steady-state. There were no statistically significant differences between dose levels of rabeprazole ($p > 0.050$) for this parameter, although there was a trend for a difference between the 10 mg vs the 40 mg dose ($p=0.07$ for AUC_{08-08}).

Table VIII.8. Mean±SD (medians) intragastric acidity AUC data for Day 7 (mmol*hr/L).

AUC interval (hrs)	Treatment			
	10 mg RBP (N=24)	20 mg RBP (N=24)	40 mg RBP (N=24)	Placebo (N=24)
08:00 – 13:00	19.6±21.5 (16.4)	12.9±23 (2.8)	7.6±14.7 (0.7)	91.1±39.7 (84)
13:00 – 19:00	5.6±9.7 (0.7)	8.3±29.8 (0.2)	1.3±5.2 (0.1)	95.5±48.7 (85.1)
19:00 – 22:00	0.1±0.1 (0.0)	0.1±0.1 (0.0)	0.0±0.02 (0.0)	11.9±12.5 (5.9)
22:00 – 08:00	129.2±84 (120.2)	109.6±67.2 (95)	76.9±58.4 (75.7)	479.9±165 (483.3)
08:00 – 08:00	155.5±90.6 (186.2)	130.9±81 (129)	85.8±64.3 (81.7)	678.5±214 (696.9)

Plasma Gastrin

Table VIII.9. provides the plasma gastrin results for the different treatments during each AUC interval. At all time intervals for AUC on Day 7, the plasma gastrin was statistically significantly higher for all doses of RBP compared to placebo ($p < 0.001$).

Table VIII.9. Mean±SD plasma gastrin AUCs on Day 7 (pmol*hr/L).

AUC interval (hrs)	Treatment			
	10 mg (N=24)	20 mg (N=24)	40 mg (N=24)	Placebo (N=24)
08:00 - 13:00	258.7±234.8	308.3±244.9[a]	383.9±306.5[b,c]	52.2±59.4
13:00 - 19:00	570.9±461.1	644.1±456.5[a]	797.6±578.6[b,d]	100.2±127.6
19:00 - 22:00	336.7±234.6	409.1±304.7[a]	486.3±344.1[b,c]	74.3±91.6
22:00 - 08:00	459.3±410.4	523.7±475.8[a]	664.2±540.7[b,c]	64.1±75.2
08:00 - 08:00	1625.7±1312.7	1885.3±1429.3[a]	2332±1729.8[b,d]	290.8±346.3

[a] $p \geq 0.102$ for 10 mg vs 20 mg
[b] $p \leq 0.005$ for 10 mg vs 40 mg
[c] $p > 0.05$ for 20 mg vs 40 mg
[d] $p < 0.05$ for 20 mg vs 40 mg

In conclusion, RBP substantially increased intragastric pH after 7 days of dosing and statistically significantly inhibited intragastric acidity at all dose levels examined. Reductions in mean integrated 24-hour intragastric acidity of 77%, 81%, and 87% were observed after the 10 mg, 20 mg, and 40 mg RBP doses, respectively, compared to placebo. RBP displayed no substantial

advantage at a dose of 40 mg, versus 10 mg or 20 mg, with respect to inhibition of intragastric acidity; although the data suggested a dose-related trend in inhibition of gastric acidity, no statistically significant differences in AUCs were found among the three doses of active drug for any of the time intervals.

RBP also statistically significantly increased plasma gastrin levels. The 40 mg RBP dose elevated the plasma gastrin levels to a greater extent than the 10 mg and 20 mg doses. Therefore, RBP could have a possible disadvantage at a dose of 40 mg with respect to elevations in plasma gastrin concentration.

3. Protocol #E044-115 - **A placebo-controlled trial to assess the effect of eight-day dosing of rabeprazole versus omeprazole on the 24-Hour intragastric acidity and plasma gastrin concentrations in young, healthy, male subjects.**

This was a single-center, double-blind, placebo-controlled, randomized, three-way crossover study to compare the effect of RBP (20 mg), OMP (20 mg), and placebo on 24-hour intragastric acidity and plasma gastrin concentrations in 24 healthy male volunteers. Subjects received each treatment for 8 days separated by a washout period of one week. Intragastric pH was monitored on an hourly basis after the first dose (Day 1) and the last dose (Day 8) of each treatment. In addition, plasma gastrin levels were determined on Day 8.

Pharmacodynamics

The mean percent of time over the 24-hour monitoring period that pH>3 or pH>4 on Day 1 and Day 8, was statistically greater for RBP than for OMP or placebo. These results are depicted in the Table VIII.10.

Table VIII.10. Summary of Mean±SD % time pH>3 and pH>4

	Treatment			p-value[a]		
	20 mg RBP (N=23)	**20 mg OMP (N=23)**	**Placebo (N=23)**	**RBP vs Placebo**	**OMP vs Placebo**	**RBP vs OMP**
pH>3/Day 1	54.6±18.5	36.7±22.4	19.1±9.2	<0.001	<0.001	<0.001
pH>3/Day 8	68.7±15.6	59.4±22.8	21.7±10.1	<0.001	<0.001	<0.008
pH>4/Day 1	44.1±20.3	24.7±22.7	7.6±7.4	<0.001	<0.001	<0.001
pH>4/Day 8	60.3±17.9	51.4±24.6	11.0±8.4	<0.001	<0.001	0.027

[a]p-value for treatment effects were obtained from ANOVA

The maximum median intragastric pH on both Day 1 and Day 8 was observed at 8 hours following RBP administration. At all AUC time intervals on Day 1 and Day 8, the intragastric acidity was statistically significantly lower for the RBP and OMP treatments compared to placebo, indicating a significant effect of the proton-pump inhibitors on intragastric acidity, both after the first dose and at steady-state. There were no statistically significant differences observed between RBP and OMP for any of the AUC intervals on Day 8.

Table VIII.11. Mean±SD intragastric acidity data for Days 1 and 8.

AUC Interval (hours)	Mean±SD AUC for intragastric acidity on Day 1 (mmol*hr/L) 20 mg RBP (N=23)	20 mg OMP (N=23)	Placebo (N=23)
08:00 - 13:00	75±64[a]	69±46[a]	133±48
13:00 - 19:00	27±42[a,b]	96±66[a]	177±56
19:00 - 22:00	2±6[a]	9±17[a]	19±16
22:00 - 08:00	236±180[a,b]	403±204[a]	596±188
08:00 - 08:00	341±242[a,b]	577±283[a]	926±257

[a]Significantly ($p<0.001$) different from placebo.
[b]Significantly ($p<0.001$) different from OMP.

AUC Interval (hours)	Mean±SD AUC for intragastric acidity on Day 8 (mmol*hr/L) 20 mg RBP (N=23)	20 mg OMP (N=23)	Placebo (N=23)
08:00 - 13:00	11±13[a]	20±33[a]	120±48
13:00 - 19:00	9±24[a]	31±47[a]	159±65
19:00 - 22:00	0.4±1.6[a]	3±10[a]	18±23
22:00 - 08:00	156±121[a]	218±161[a]	565±202
08:00 - 08:00	177±147[a]	271±229[a]	826±278

[a]Significantly ($p<0.001$) different from placebo.

Plasma Gastrin

At every time interval during the 24 hours after dosing on Day 8, the mean partial and total AUCs for plasma gastrin with RBP treatment were significantly greater than those observed for OMP and placebo. The mean AUCs for OMP were also found to be significantly greater than placebo at all time intervals. Plasma gastrin AUC results are displayed in Table VIII.12.

Table VIII.12. Mean±SD plasma gastrin AUC data (pmol*hr/L).

	Treatment			p-value[a]		
Day 8	20 mg RBP (N=22)	20 mg OMP (N=22)	Placebo (N=22)	RBP vs Placebo	OMP vs Placebo	RBP vs OMP
08:00-13:00	360±237	229±141	54±34	<0.001	<0.001	0.001
13:00-19:00	592±408	368±241	76±59	<0.001	<0.001	0.001
19:00-22:00	403±272	249±142	72±53	<0.001	<0.001	<0.001
22:00-08:00	590±473	343±286	56±30	0.001	<0.001	0.003
Total 24 hr	1944±1345	1189±770	258±164	<0.001	<0.001	0.001

[a]p-value for treatment was obtained from ANOVA

In conclusion, the mean percent of time that gastric pH>3 and gastric pH>4 over a 24-hour time period on Day 1 and Day 8, were statistically significantly greater for RBP treatment as compared with either OMP or placebo. In addition, intragastric acidity was statistically significantly reduced, with total $AUC_{08\text{-}08}$ (24-hour values) after eight days resulting in 79% and 69% reductions during administration of RBP and OMP, respectively, in comparison to values obtained during placebo administration. However, there were no significant differences observed between RBP and OMP for reduction of intragastric acidity at steady-state (Day 8). Mean plasma gastrin concentration curves following RBP and OMP were higher than those following placebo. In addition, gastrin concentrations were statistically significantly greater after RBP administration compared to OMP.

Reviewer's Comments:
The manner of reporting the "% of time that gastric pH was greater than" a given value is very misleading when using an intermittent pH monitoring method. The reader is left with the impression that the values reflect the percent of **time** that gastric pH is maintained above a specified pH, when the values are really an indication of the number of **recordings** that gastric pH is maintained above a specified value. Furthermore, a correlation between the percent of time gastric pH>3 or pH>4 and clinical efficacy has not been validated. Finally, almost 40% (9/24) of the individual subjects in this study had lower values for gastric acidity during OMP treatment when compared to RBP treatment on either Days 1 or 8.

4. Protocol #L001-A - Rabeprazole effects on esophageal and gastric pH after single and multiple oral doses in patients with gastroesophageal reflux disease.

This was a single-center, double-blind, randomized, two-way crossover study to examine the effects of single and multiple doses of RBP (20 and 40 mg) on esophageal and gastric pH in 20 male and female patients with GERD. RBP was administered once daily for 7 days with a 7-10 day washout interval between treatments.

Pharmacodynamics

Reflux Time

Both RBP doses reduced reflux time, however the differences between the 20 mg and 40 mg doses were not statistically significant. On Day 8, reflux time remained reduced for both RBP doses, but had returned to values slightly higher than those observed during the first day of dosing. All comparisons between the Days and baseline were statistically significant ($p<0.03$).

Table VIII.13. Summary of Mean±SD reflux time (%).

	20 mg RBP (N=20)	40 mg RBP (N=20)
Baseline	24.7±18.8	23.7±20.8
Day 1	12.7±18.2	7.0±10.4
Day 7	5.1±10.5[a]	2.0±4.7
Day 8	16.7±17.7[b]	12.0±14.6[b]

[a] p=0.036 Day 7 vs Day 1 for 20 mg dose.
[b] p=0.002 Day 8 vs Day 7 for 20 and 40 mg dose.

On the Baseline Monitoring Day, Dosing Days 1 and 7, and Day 8, both RBP doses were associated with lower mean reflux time in Period 2 than in Period 1. Additionally, five patients no longer met the GERD disease diagnosis criteria (reflux time >5% of 24-hour monitoring period) at baseline for Period 2. However, the treatment-by-period interaction effect was not statistically significant, and there was no indication of a dose (or differential treatment) carryover effect. For completeness, reflux time was analyzed for the subset of patients who did meet the GERD disease diagnosis criteria at baseline for Period 2. The results of the statistical analysis were essentially unchanged.

Effective Reduction in Reflux Time

There were no statistically significant differences between the 20 mg dose and the 40 mg dose for this parameter. On Day 1, effective reductions in reflux time (≤5% of 24-hour monitoring time) were observed in 60% of patients taking the 40 mg RBP dose versus 45% taking the 20 mg dose (p=.453). By Day 7, effective reductions in reflux time were observed in 90% of patients on the 40 mg RBP dose versus 75% on the 20 mg dose (p=.250).

At study entry, reflux times of all patients satisified GERD criteria. By Day 1, reflux times no longer met GERD diagnostic criteria in 75% of patients taking 20 mg RBP or for 80% taking the 40 mg dose. These percentages rose to 90% for each dose after 7 days of treatment. Twenty-four hours after the last dose of study drug (Day 8), reflux times had not yet returned to GERD diagnostic levels in 50% of patients taking the 20 mg RBP dose and for 65% taking 40 mg RBP. There were no statistically significant differences between the two doses in the proportions of patients satisfying GERD criteria at any timepoint.

Reflux Episodes

The differences between doses in reducing the number of reflux episodes were not statistically significant. On Day 8, the number of reflux episodes remained reduced for both RBP doses. Treatment-by-period interactions were not statistically significant and the direction of dose effects generally appeared consistent for both Periods. Results are summarized in Table VIII.14.

Table VIII.14. Mean±SD number of reflux episodes.

	20 mg RBP (N=15)	40 mg RBP (N=15)
Baseline	135.8±97.8	133.8±103.7
Day 1	84.3±110.9[a]	41.7±31.2[b]
Day 7	21.8±32.9[b,c]	7.5±9.8[b]
Day 8	65.9±59.3[b]	46.8±49.1[b,d]

[a]p=0.05 vs Baseline
[b]p<0.001 vs Baseline
[c]p=0.018 Day 7 vs Day 1 for 20 mg dose.
[d]p=0.04 Day 8 vs Day 7 for 40 mg dose.

Reflux Episodes >5 Minutes

The differences between doses were not statistically significant. By Day 8, the number of reflux episodes >5 minutes remained reduced for both RBP doses but had returned to values similar to the first day of dosing. Treatment-by-period interactions were not statistically significant and the direction of dose effects generally appeared consistent for Period 1 and Period 2. Results are summarized in Table VIII.15.

Table VIII.15. Mean±SD number of reflux episodes >5 minutes.

	20 mg RBP (N=15)	40 mg RBP (N=15)
Baseline	15.8±11.3	12.6±9.0
Day 1	6.2±8.7[a]	2.9±3.7[a]
Day 7	2.0±4.4[a]	0.8±2.0[a]
Day 8	6.7±6.4[a]	6.4±9.6[a,b]

[a]p≤0.006 vs Baseline
[b]p=0.012 Day 8 vs Day 7 for 40 mg dose.

Number of Patients With No Reflux Episodes >5 Minutes

At baseline, all 20 patients in the study experienced at least one reflux episode of more than 5 minutes duration. Nine and 15 patients (45% and 75%) taking 20 mg and 40 mg RBP, respectively, had no reflux episodes >5 minutes by the seventh day of dosing. This difference was statistically significant (p=0.041).

Gastric pH

Both RBP doses statistically significantly increased mean gastric pH. On both Dosing Days 1 and 7, higher mean gastric pH values were seen with the 40 mg RBP dose than with the 20 mg dose, and these differences were statistically significant (see Table VIII.16. below). On Day 8 mean gastric pH remained elevated for both RBP doses. Median gastric pH values yielded very similar results.

Table VIII.16. Mean±SD gastric pH.

	20 mg RBP (N=15)	40 mg RBP (N=15)
Baseline	1.86±0.48	2.01±0.49
Day 1	3.71±1.35[a]	4.37±0.85[a]
Day 7	4.17±1.02[a,b]	4.65±1.12[a]
Day 8	4.01±1.14[a]	4.23±1.14[a,c]

[a]p<0.001 vs Baseline
[b]p=0.034 Day 7 vs Day 1 for 20 mg dose.
[c]p=0.017 Day 8 vs Day 7 for 40 mg dose.

Plasma Gastrin Concentration

The difference between the 20 mg and 40 mg RBP doses for AUC_{0-8} on Dosing Day 7 was statistically significant (p=0.022). The plasma gastrin AUC_{0-8} values and the results of the statistical analyses are summarized in Table VIII.17.

Table VIII.17. Mean±SD plasma gastrin AUC_{0-8}.

	20 mg RBP (N=15)	40 mg RBP (N=15)
Day 1	537.8±266.7	604.7±269.4
Day 7	781.2±405.5[a]	980.8±573.2[a]
Day 8	719.9±388.1[b]	761.7±415.0[c]

[a]p<0.001 Day 7 vs Day 1
[b]p=0.004 Day 8 vs Day 1 for 20 mg dose.
[c]p=0.013 Day 8 vs Day 7 for 40 mg dose.

In conclusion, after both 20 mg and 40 mg doses of RBP, there were statistically significant reductions in esophageal reflux time and the number of reflux episodes (total and those >5 minutes) compared to baseline values, after a single dose and at steady-state. In addition, statistically significant increases were observed for intragastric pH for both RBP doses at Day 1 and Day 7. There were no statistically significant differences between the 40 mg RBP dose compared to the 20 mg dose with regards to reduction in reflux time or number of reflux episodes, even though the gastric pH for the 40 mg RBP dose was significantly greater than the 20 mg dose at both Days 1 and 7.

There were statistically significant elevations observed in plasma gastrin levels after both doses of RBP, and the 40 mg RBP dose produced greater increases by steady-state compared to the 20 mg dose. This was considered by the sponsor to be a possible disadvantage.

Reviewer's Comments with regards to American/European PD Studies:

Overall, these studies were better designed and executed than the PD studies performed in Japan. However, there are some caveats that should be considered when interpreting the results. The PD parameters assessed in these studies inherently contain large intra- and interindividual variability.

Intragastric pH can be monitored intermittently or on a continuous basis. All of these studies used intermittent pH monitoring (a specified number of measurements per hour) with the exception of the GERD study, which used continuous, 24-hour pH monitoring. Neither method has been validated to show superiority. Furthermore, opinion differs as to the optimal position for placement of the pH electrodes within the stomach in order to monitor clinically relevant gastric pH changes. Perhaps most importantly, correlations between changes in gastric pH and either gastrointestinal symptoms or clinical efficacy have not been validated.

Conclusions from the PD Studies

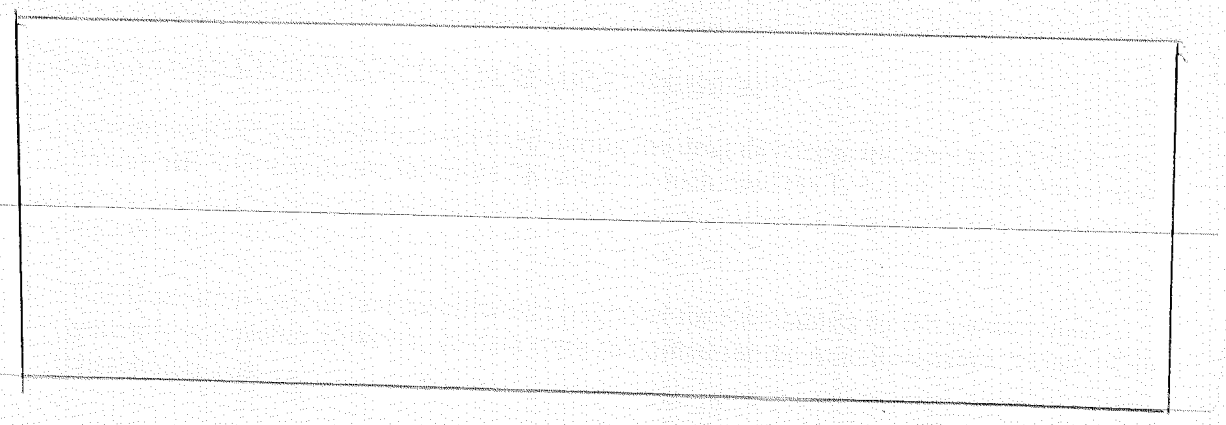
The eight PD studies discussed above are summarized in Table 7 in Appendix I. In general, RBP was effective in reducing intragastric acidity, increasing gastric pH, and increasing the percent of time that gastric pH>3 or pH>4 after single and multiple doses of 20 or 40 mg in healthy subjects. (The effectiveness of 10 mg doses was less clear). RBP was effective in reducing gastric acidity in GU, DU, and GERD patients as well. In addition, there were significant reductions in both esophageal reflux time and the number of episodes after single and multiple doses of 20 and 40 mg RBP in GERD patients. RBP doses of 40 mg did not appear to provide increased efficacy, however, did result in greater increases in serum gastrin levels compared to the 20 mg dose. Overall, there were small differences in PD parameters between OMP and RBP.

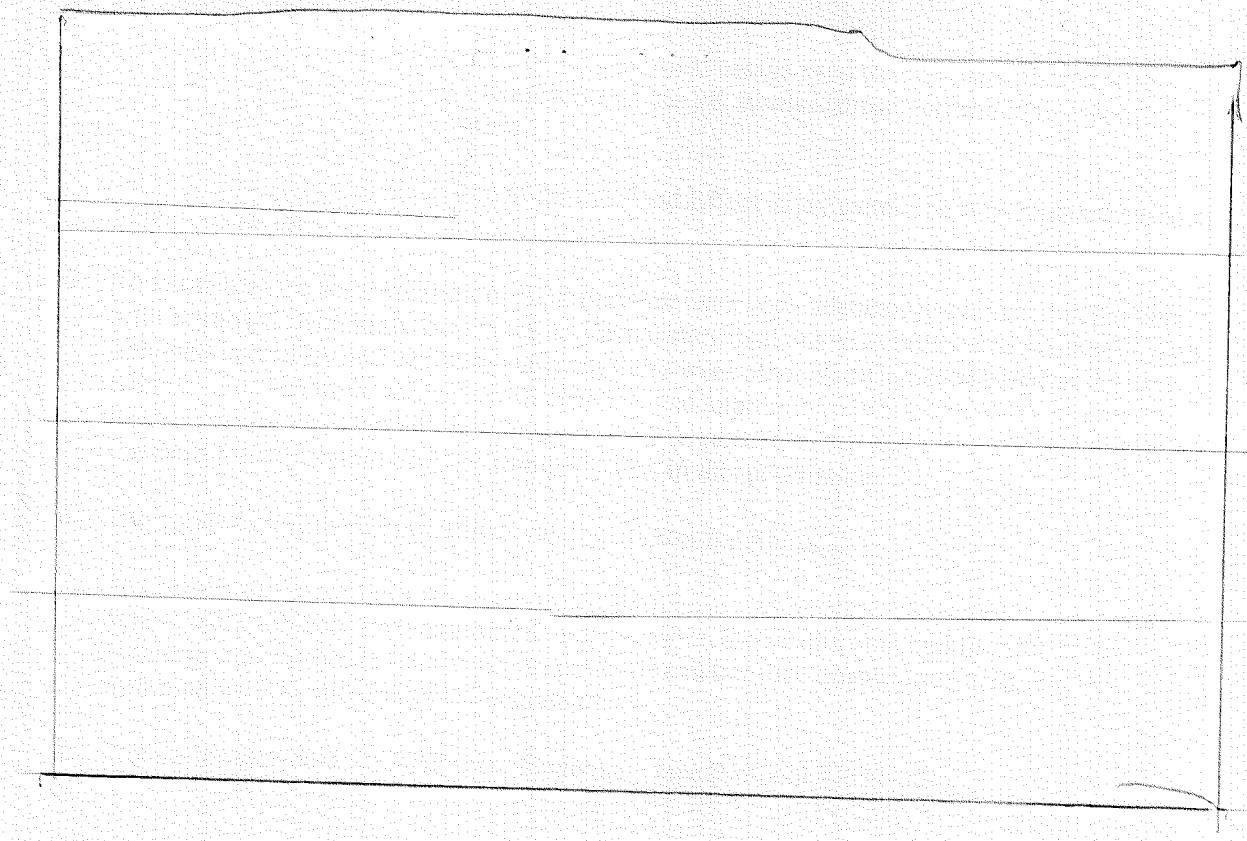
IX. PK/PD RELATIONSHIPS

Overall, there were a very limited number of studies submitted to this NDA for which both plasma RBP concentration-time data and PD data were obtained. In most of these studies, the PK data were either unreliable or the plasma RBP concentrations were below the assay LOQ by the time the PD assessment was performed. Only one study formally examined a PK/PD relationship (see discussion under **Protocol #A001-002, Multiple-Dose Studies**), and it was concluded that no PK/PD correlation was present for the parameters that were assessed.

X. SAFETY ISSUES

RBP was well-tolerated by the vast majority of subjects based on physical examination, clinical laboratory tests, ECGs, vital signs and assessment of adverse events. Serious adverse events and clinically significant laboratory changes were reported in the renally and hepatically impaired subjects, however, most of these were considered to be a function of the disease state and not related to the administration of RBP. Administration of RBP by the intravenous route resulted in more AEs compared to the oral route, but all of these were considered to be mild in nature. Adverse events reported in the drug interaction studies were attributed to the co-administered drug rather than RBP.





XII. COMMENTS TO BE SENT TO THE SPONSOR

1. Submit the results for the Acid Resistance portion of the Dissolution Testing for 12 individual tablets of RBP. In addition, provide the means±SD and % coefficient of variation.

2. A well-designed and well-controlled Food Effect Study should be performed, which is consistent with the guidelines set forth in the FDA draft "Guidance for Industry, Food-Effect Bioavailability and Bioequivalence Studies," October, 1997.

3. Reanalyze the data from the liver cirrhosis study (Protocol #A001-004) to assess whether there were statistically significant differences in pharmacokinetic parameters between healthy subjects and subjects with cirrhosis.

4. Perform a study to assess the in vitro protein-binding of RBP, covering the relevant concentration range.

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

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DRAFT LABELING

APPENDIX II

INDIVIDUAL STUDY REPORTS

BIOEQUIVALENCE STUDIES

TITLE: A crossover study to evaluate the bioequivalency of 10 mg and 20 mg E3810 tablets in healthy male volunteers

Protocol Number: E3810-J081-009

Study Date: February, 1990

OBJECTIVE: to evaluate the BE of 2x10 mg tablets and 1x20 mg tablet RBP in healthy male volunteers

METHODS:

Study Design: randomized, two-treatment, two period, two-way crossover

Study Population: 24 healthy male volunteers

Treatment and Drug Administration: 12 subjects received 2x10 mg of RBP and 12 subjects received 1x20 mg RBP with 120 ml water after an overnight fast. Subjects remained fasting until 5 hours after dosing. After a one-week washout period, subjects were crossed over to the opposite treatment.

Study Drug Supplies:

10 mg enteric-coated RBP tablets; #K9X0600. ***This was not the to-be-marketed formulation or strength..***

20 mg enteric-coated RBP tablets; #K012400. ***This is the to-be-marketed formulation.***

Biological Sampling: Blood was collected prior to dosing and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, and 24 hours after RBP administration.

PK Analysis: Non-compartmental PK parameters were calculated for $AUC_{0\text{-}24}$, Cmax, and tmax using standard methods.

Statistical Methods:

ANOVA was performed on untransformed and log-transformed values of $AUC_{0\text{-}24}$ and Cmax. The Two One-sided Tests Procedure and the calculation of the 90% confidence intervals were performed to evaluate BE.

Analytical Methods: Pre-analytical validation was performed by Eisai Co., Ltd., Tokyo. The analytical assays of study samples were performed by [redacted] using [redacted] with [redacted] Assay validation parameters are provided below.

Pre-study Validation (5/88):		
	Curve	Quality Control
Linearity	>0.999 at 5-400 ng/ml	-
LOQ	5 ng/ml	-
Interday Precision	<15% CV	ND
Interday Accuracy	NR	ND
Intraday Precision	<10% CV	ND
Intraday Accuracy	NR	ND
Specificity: No blank [redacted] nor [redacted] samples submitted.		
Recovery: Ranged from 112% at 5 ng/ml to 86% at 400 ng/ml with <7% CV.		
Stability: 100% residual at room temperature for 30 min, 101% residual at 20°C for 10 months, >95% at 98 ng/ml after 4 freeze/thaw cycles.		
In-Study Validation (2/90-7/90):		
	Curve	Quality Control
Linearity	>0.995 from 30.7-122.7 ng/ml >0.995 from 122.7-981.5 ng/ml	-
LOQ	10 ng/ml	-
Interday Precision	NR	<3% CV at 196 ng/ml
Interday Accuracy	NR	100% at 196 ng/ml
Intraday Precision	NR	<10% CV at 196 ng/ml
Intraday Accuracy	NR	>96% at 196 ng/ml
Specificity: [redacted] did not reveal potential interference. Also included were 1 QC (245 ng/ml), 1 LOQ, and 2 individual subject sample [redacted] which were acceptable.		

Safety:
Assessed by adverse events, clinical laboratory tests, physical examinations, ECGs, and vital signs.

RESULTS:

Demographics:
All subjects were Japanese males ranging in age from 20-26 years. Mean weights and heights were 60.2 kg and 169.4 cm, respectively. Baseline characteristics were similar for the two treatment groups.

Pharmacokinetics:
The mean±SD PK parameters for RBP and the results of the BE analysis are provided in Table 1.

Table 1. Mean±SD PK parameters and BE analysis.

	2x10 mg (N=24)	1x20 mg (N=24)	Geometric Mean Ratio (%) (2x10mg/1x20mg)	90% CI 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%)	-	-

Although $AUC_{0-\infty}$ was not determined in this study, no subject had any detectable plasma levels of RBP at 24 hours for either treatment. Furthermore, the majority of the last detectable plasma concentrations were near the assay LOQ for most of the subjects, therefore, values for AUC_{0-24}

and $AUC_{0-\infty}$ were not likely to be significantly different. The data in this study indicates that 2x10 mg RBP tablets were not BE to a 1x20 mg RBP tablet, according to the Two One-Sided Tests Procedure and 90% confidence interval range of 80-125% using log-transformed data for AUC_{0-24} and Cmax. The results of the Wilcoxon signed-ranks test for tmax revealed no significant differences ($p>0.437$) between the two treatment groups.

Safety:
All symptoms reported were mild, and none of them were judged to be drug related. No clinically significant abnormal values or changes in vital signs or clinical laboratory tests were observed during the course of the study.

CONCLUSIONS:
RBP, whether administered as two 10 mg tablets or one 20 mg tablet, was well tolerated by all subjects, as evidenced by the lack of drug-induced effects on vital signs, physical examination, electrocardiograms and clinical laboratory test results.

However, the results of this study indicate that, under fasting conditions, 2x10 mg RBP tablets were not BE to a 1x20 mg RBP tablet according to the Two One-Sided Tests Procedure and 90% confidence interval range of 80-125% using log-transformed data for AUC_{0-24} and Cmax.

REVIEWER'S COMMENTS:
1. Pre-study analytical validation was inadequate and/or unacceptable. Although the in-study validation provided some additional data, there were still inadequacies; i.e., QC samples examined at only one concentration, no precision/accuracy data for calibration curve concentrations, no chromatograms provided from individual subjects, change in the LOQ of the assay without validation, etc.
2. Values for half-life and kel were not reported.
3. The 10 mg RBP tablets were used in one clinical trial, which was not considered to be pivotal. They were also administered in PK studies #A001-001 and #A001-002, which were the pivotal single-dose and multiple-dose studies. However, this may be of little significance, as 10 mg was the only tablet strength used in these two studies.

APPEARS THIS WAY
ON ORIGINAL