dosage adjustment is recommended for patients with renal insufficiency. The following table provides the mean and median PK parameters for each treatment regimen.

Table VII.20. Mean±SD [medians] PK parameters.

	Healthy subjects (N=10)	Renal Patients (N=10)	
		During Hemodialysis	Post-Hemodialysis
PK Parameter	Means±SD [median]	Means±SD [median]	Means±SD [median]
AUC_{0-24} (ng*hr/ml)	613±483 [482]	422±293 [441]	370±287 [217]
Cmax (ng/ml)	347±238 [221]	236±204 [191]	224±191 [116]
Tmax (hr)	3.5±0.7 [3]	3.2±0.8 [3]	2.9±1.0 [3]
Half-life (hr)	0.8±0.5 [0.6]	1.0±0.9[a] [0.6]	3.6±8.0[a] [0.8]
Cl_T (ml/min)	817±442 [820]	1640±1666 [789]	1581±1109 [1533]

[a]These values were recalculated by the reviewer; see text for explanation.

2. Protocol #A001-004 - A pilot study of the safety, tolerance, and pharmacokinetics of E3810 in healthy male volunteers and in men with chronic hepatic cirrhosis.

This was a single-center, open-label, parallel-cohort study to assess the safety, tolerance, and PKs of RBP, after a single oral dose of 20 mg to 13 healthy males and 10 males with stable, chronic compensated cirrhosis of the liver.

For cirrhotic subjects compared to healthy subjects, AUC_{0-24} was more than doubled, C_{max} was approximately 50% greater, the elimination half-life was 2- to 3-fold higher, and the Cl_T was decreased to less than half. These results are consistent with slower elimination of the drug in subjects with impaired liver function, who are likely to have impaired drug metabolism capabilities. Mean PK parameters for both groups are provided in Table VII.21.

Table VII.21. Mean±SD for PK parameters in healthy and cirrhotic subjects.

Parameter	Healthy Subjects (N=13)	Cirrhotics (N=10)
AUC_{0-24} (ng*hr/ml)	809±544	1776±496
Cmax (ng/ml)	401±246	635±199
Tmax (hr)	3.7±1.0	4.6±2.8
Half-life (hr)	1.7±1.7	3.7±2.2
Cl_T (ml/min)	550±260	201±57

Reviewer's Comments:
Although the sponsor has concluded that accumulation of RBP is unlikely to occur with once daily dosing in these patients despite the increase in half-life to more than 3 hr, an assessment is difficult to make based on administration of only a single dose. Indeed, some individuals had half-life values which were substantially greater than 3 hours (range: 1.7-8.3 hours), and could conceivably experience drug accumulation with multiple dosing.

No formal statistical results were reported for the differences observed in PK parameters between the two cohorts. It is recommended that the sponsor provide results for any statistical analyses of the differences in PK parameters between the healthy and cirrhotic cohorts. The Medical Officer will be requested to evaluate whether adjustments in RBP administration will be necessary for this population.

3. Protocol #A001-108 - A study of the safety, tolerance, pharmacokinetics, and pharmacodynamics of rabeprazole sodium in healthy volunteers and in subjects with impaired hepatic function.

This was a two-center, open-label, multiple-dose study to assess the safety, PKs, and PDs after a single daily oral 20 mg dose of RBP to 12 healthy volunteers and to subjects with impaired hepatic function (Grade A or B as defined by the Child-Pugh Classification). The mean PK parameters of RBP for the healthy and hepatically impaired patients are displayed in Table VII.22. below.

Table VII.22: Summary of Mean±SD PK parameters for RBP.

Parameter	Healthy[a,c]	Hepatic[a] (N=12)	p-value[b]	
			Log-transformed	Untransformed
AUC_{0-24} (ng*hr/ml)	796.1±565.3	1175.6±713.9	0.225	0.175
Cmax (ng/ml)	382.7±274.5	447.0±323.6	0.753	0.614
Tmax (hr)	4.9±3.6	2.3±0.8	0.049	0.049
$AUC_{0-\infty}$ (ng*hr/ml)	1093±541.8	1331.6±704.3	0.628	0.452
Kel (1/hr)	0.39±0.18	0.26±0.31	0.069	0.342
Half-life (hr)	2.1±0.8	12.3±18.3	0.069	0.164
CL_{oral} (L/hr/kg)	0.33±0.23	0.36±0.42	0.353	0.353
Vd (L/kg)	0.94±0.66	4.84±6.97	0.121	0.162

[a]Arithmetic mean from the untransformed data.
[b]ANOVA for all parameters except Tmax and CL_{oral} (Wilcoxon Rank Sum Test).
[c]N=12 for AUC_{0-24}, Cmax, and Tmax and N=7 for $AUC_{0-\infty}$, kel, half-life, CL, and Vd.

Compared to healthy subjects, the hepatically impaired subjects had larger AUC and Cmax values, increased volume of distribution, and a terminal half-life that was longer by approximately 10 hours. However, mean Cl/F values were very similar. Although differences in the PK parameters between the cohorts were noted, results of the ANOVA, both original scale as well as the log-transformed data, indicated that no statistically significant differences existed between healthy volunteers and hepatically impaired subjects ($p>0.05$ for all parameters). Even though the difference between the cohorts for the mean values of half-life was large, the lack of a statistically significant difference was due to the high variability in this parameter for the hepatically impaired cohort. For example, two subjects in this group had half-lives of 22 hours and 65 hours, respectively. The Medical Officer will be requested to evaluate whether adjustments in RBP administration are necessary for this population.

4. Protocol #A001-112 - An open-label, multidose pharmacokinetic comparison of 20 mg rabeprazole sodium in normal, healthy elderly and young volunteers.

This was open-label, single-center, parallel-group, two-cohort study to assess the PKs of RBP in normal, healthy, male and female, young and elderly subjects. RBP was administered as a single oral 20 mg dose for 7 days. Twenty volunteers were recruited for each cohort. The table below presents the PK parameters from Day 7, and the p-values from the statistical analysis for each PK parameter by cohort.

Table VII.23. Mean±SD PK parameters for RBP by cohort.

Parameter	Young Cohort (N=20)	Elderly Cohort (N=20)	p-value*
AUC_{0-T} (ng*hr/ml)	631.2±273.8	1194.6±398.8	<0.0001
$AUC_{0-\infty}$ (ng*hr/ml)	645.1±276.8	1210.8±403.8	<0.0001
Cmax (ng/ml)	426.9±144.0	668.9±215.6	0.0002
Cmin (ng/ml)	0±0	0±0	-
Tmax (hr)	3.5±0.9	2.9±0.8	0.0163
kel (1/hr)	0.86±0.30	0.62±0.19	0.0055
Half-life (hr)	0.9±0.4	1.2±0.3	0.0228

*p-values obtained from Student's t-test for all PK parameters except Tmax (Wilcoxon Signed-Rank Test)

The half-life of RBP was short in both the young and elderly cohorts, although was increased in the elderly by about 30%. Mean values for the PK parameters and the results of the statistical analysis indicated that the subjects in the elderly cohort exhibited significantly greater AUC (approximately double) and Cmax values, and shorter Tmax values, than did the subjects in the younger cohort. There were no detectable quantities of RBP in the plasma of the young subjects prior to dosing on Days 5, 6, or 7. There were measurable levels of RBP in two of the elderly subjects prior to the Day 6 dose, however, the two subsequent 24-hour post-dose concentrations (Time 0 hr, Day 7 and Time 24 hr, Day 7) were below the LOQ. Therefore, it was concluded that there was no evidence of accumulation following daily dosing of RBP for 7 days.

In conclusion, there were statistically significant differences for the PKs of RBP after 7 daily doses when young subjects were compared to elderly subjects. However, since the elderly did not demonstrate any additional risk of adverse effects nor accumulation of RBP, an adjustment in dose is probably not required.

5. Gender Analysis

A gender analysis was performed using the results of the pivotal BE study (#A001-114), however, it was subsequently discovered that the $AUC_{0-\infty}$ values used for this analysis were not valid. The sponsor has recalculated these values (submitted on December 11, 1998) and will be requested to reanalyze this data for gender differences.

6. Ethnicity Analysis

Reports of RBP PKs were utilized to obtain data for $AUC_{0-\infty}$, Cl/F, body weight, and Cl/F/BW in Japanese and American subjects. For purposes of consistency, maximization of data, and to limit variables, the following criteria were used: 1) data from single-dose studies, 2) doses of 10, 20, and 40 mg, 3) healthy, male subjects, and 4) $AUC_{0-\infty}$. PK data were analyzed using an unpaired t-test. Table 6, included in Appendix I, provides the results of the statistical analysis. Overall, it appears that male Japanese subjects can be predicted to exhibit greater $AUC_{0-\infty}$ values than their American male counterparts, however, the validity of the data from Japanese subjects is tentative due to the analytical assay concerns and uncertainties regarding the BA of the RBP formulations used in those studies (see, IV. BE Studies, pg. 8-11, and VI. Analytical Assays and Validation, pg. 13).

G. Drug Interaction Studies

1. Protocol #A001-101 - **A study to evaluate the effects of rabeprazole sodium on the pharmacokinetics of warfarin.**

2. Protocol #A001-103 - **A study to evaluate the effects of rabeprazole sodium on the pharmacokinetics of ketoconazole.**

3. Protocol #A001-105 - **A study to evaluate the effects of rabeprazole sodium on the pharmacokinetics of theophylline.**

These 3 studies were conducted in normal, healthy, male volunteers using a similar study design. The subjects received a single dose of the drug being investigated in Period 1 as described in the table below:

Table VII.24. Study Design for three drug interaction studies.

Study No.	Period 1	Period 2	Number of subjects
A001-101	0.75 mg/kg warfarin	20 mg RBP or placebo daily for 14 days plus 0.75 mg/kg warfarin on Day 8	21
A001-103	400 mg ketoconazole	20 mg RBP or placebo daily for 8 days plus 400 mg ketoconazole on Day 8	19
A001-105	250 mg theophylline	20 mg RBP or placebo daily for 8 days plus 250 mg theophylline on Day 8	25

Following a washout period (7 days for volunteers receiving warfarin and ketoconazole and 3 days for theophylline), volunteers were randomized to receive either 20 mg RBP or placebo with the corresponding dose of the drug of interest given on Day 8. In addition to PK parameters, PT was also evaluated in the warfarin study as a PD endpoint. Results for each study are provided and discussed below.

Warfarin Study: One subject was dropped due to a prolonged PT, therefore, was excluded from the PK data analysis. Comparison of the changes in PK parameters for both warfarin enantiomers between Period 1 and Period 2 did not reveal any statistically significant differences ($p>0.1$ for all parameters) between the RBP-treated subjects and the placebo-treated subjects.

Table VII.25. Mean±SD PK parameters for R-warfarin.

PK Parameter	RBP group Period 1 (N=10)	RBP group Period 2 (N=10)	Placebo group Period 1 (N=10)	Placebo group Period 2 (N=10)
AUC_{0-T} (ng*hr/ml)	194312±17858	322531±400064	212702±31506	207601±35161
$AUC_{0-\infty}$ (ng*hr/ml)	217059±25549	359038±436260	242942±46601	235743±48779
Cmax (ng/ml)	3782±159	5935±6492	4084±509	4154±623
Tmax (hr)	1.3±0.5	1.1±0.3	1.4±1.0	1.5±1.0
Kel (1/hr)	0.01±0.00	0.02±0.01	0.01±0.00	0.01±0.00
Half-life (hr)	50.0±7.9	48.4±12.3	53.0±9.5	51.0±8.7

Note: results for S-warfarin are similar.

The PD responses based on prothrombin time were similar for both treatment periods for the RBP-treated subjects and the placebo-treated subjects; there were no statistically significant differences ($p>0.06$). PD parameters are summarized in Table VII.26.

Table VII.26. Mean±SD PD parameters – prothrombin time.

PD Parameter	RBP group Period 1 (N=10)	RBP group Period 2 (N=10)	Placebo group Period 1 (N=11)	Placebo group Period 2 (N=10)
$AUC_{0\text{-}72}$ (sec*hr)	499±99	429±96	538±129	413±85
Pmax (sec)	12±2	11±2	13±3	10±2
Tmax (hr)	48±0	50±5	49±4	49±4

There were no statistically significant differences in any of the PK or PD parameters for warfarin when baseline values were compared to those obtained during either RBP or placebo administration. These findings suggest that there was no interaction between RBP and warfarin when co-administered.

Reviewer's Comment:
Single-dose administration of warfarin is not representative of the typical clinical situation, during which multiple doses of warfarin are administered. The Medical Officer will be requested to assess the need for an additional multiple-dose warfarin-RBP drug interaction study.

Ketoconazole Study – The PK results are displayed in the table below. There were statistically significant treatment differences observed between the RBP and placebo groups in the changes from Period 1 to Period 2 for $AUC_{0\text{-}T}$ (p=0.024), $AUC_{0\text{-}\infty}$ (p=0.026), and Cmax (p=0.040). No statistically significant differences were observed for any of the other PK parameters.

Table VII.27. Mean±SD PK parameters for ketoconazole

PK Parameter	RBP group Period 1 (N=10)	RBP group Period 2 (N=10)	Placebo group Period 1 (N=9)	Placebo group Period 2 (N=9)
$AUC_{0\text{-}T}$ (µg*hr/ml)	57.4±21.8	39.3±22.7	50.9±20.2	54.3±19.9
$AUC_{0\text{-}\infty}$ (µg*hr/ml)	57.8±21.8	39.7±22.7	51.5±20.6	54.7±20.0
Cmax (µg/ml)	10.0±2.9	6.8±3.2	9.1±2.5	9.0±3.1
Tmax (hr)	2.3±1.1	2.7±0.7	2.1±0.3	2.30±0.9
kel (1/hr)	0.30±0.09	0.25±0.08	0.29±0.08	0.26±0.07
Half-life (hr)	2.4±0.6	3.1±1.3	2.6±0.8	2.8±0.5

The significant differences that were observed indicate that some type of interaction occurred between RBP and ketoconazole, resulting in an approximately 30% decrease in ketoconazole bioavailability. This interaction is predictable on the basis of RBP's known potent antisecretory effects, and the requirement for gastric acid to maximize the BA of ketoconazole. The sponsor reccomended that consideration be given to altering the ketoconazole dosing regimen and that patients be appropriately monitored for therapeutic response to ketoconazole, when concurrent ketoconazole and RBP therapy is indicated. This recommendation has been included in the package insert.

Theophylline Study - The following table provides the PK parameters obtained for theophylline. There were no statistically significant treatment differences ($p>0.10$) between the RBP and placebo groups in the changes from Period 1 to Period 2 for any of the PK parameters, indicating a lack of an interaction between these two drugs.

Table VII.28. Mean±SD PK parameters for theophylline.

PK Parameter	RBP group Period 1 (N=12)	RBP group Period 2 (N=12)	Placebo group Period 1 (N=13)	Placebo group Period 2 (N=13)
AUC_{0-T} (μg*hr/ml)	82.0±19.2	81.2±15.7	82.3±12.8	84.7±10.4
$AUC_{0-\infty}$ (μg*hr/ml)	89.0±25.7	87.9±20.4	88.0±15.6	91.1±13.3
Cmax (μg/ml)	7.8±1.6	7.9±1.4	7.9±1.0	8.1±1.0
Tmax (hr)	1.4±0.9	1.1±0.5	1.5±0.9	1.1±0.5
kel (1/hr)	0.10±0.02	0.10±0.02	0.10±0.02	0.10±0.02
Half-life (hr)	7.3±1.9	7.5±1.7	7.0±1.6	7.4±1.5

4. Protocol #A001-102 - A study to evaluate the effects of rabeprazole sodium on the pharmacokinetics of digoxin.

This was a single-center, double-blind, randomized, parallel-group, drug interaction study in 16 normal, healthy, males. Subjects received an initial 0.375 mg oral dose of digoxin on Day 1 of the study, followed by daily 0.25 mg doses on Days 2-24. On Day 11, subjects were randomized to receive either 20 mg RBP or placebo, which was administered daily (in addition to the digoxin dose) through Day 24.

Statistically significant treatment differences ($p<0.05$) between the RBP and placebo groups were observed in the changes from Period 1 to Period 2 for AUC_{0-24} (19% increase) and Cmax (29% increase). There were no significant differences between the treatment groups with respect to Tmax, kel, half-life, or Cl_{renal} ($p>0.1$).

Table VII.29. Mean±SD PK parameters for digoxin.

PK Parameter	RBP group Period 1 (N=9)	RBP group Period 2 (N=9)	Placebo group Period 1 (N=7)	Placebo group Period 2 (N=7)
AUC_{0-24} (ng*hr/ml)	15.6±4.8	18.6±4.5	15.8±4.6	14.6±4.3
Cl_{renal} (L/hr)	11.2±2.9	9.1±2.3	10.9±2.0	10.7±2.6
Cmax (ng/ml)	1.5±0.3	1.9±0.5	1.6±0.5	1.5±0.4
Tmax (hr)	1.1±0.7	0.9±0.2	1.4±0.9	1.2±0.6
Kel (1/hr)	0.02±0.01	0.02±0.01	0.02±0.01	0.02±0.01
Half-life (hr)	35.7±19.4	35.5±12.9	30.7±8.2	39.0±16.9

The results indicated that an interaction occurred and was consistent with an increase in the absorption of digoxin when co-administered with RBP. This increase in serum digoxin concentrations would not be clinically significant in most patients, however, in patients with severely compromised congestive heart failure or impaired renal function, the effect could be significant. The sponsor recommended that patients who require concurrent therapy with RBP and digoxin, have serum digoxin concentrations monitored following initiation of RBP therapy and, if necessary, titration of the digoxin dose. This recommendation has been included in the package insert.

5. Protocol #A001-104 - **A study to evaluate the effects of rabeprazole sodium on the pharmacokinetics of phenytoin.**

This was a single-center, double-blind, randomized, parallel-group, drug interaction study in 24 healthy, adult males. During Period 1, each subject received a single oral 200 mg dose of phenytoin on Days 1-3. On Day 4, 250 mg of phenytoin was administered intravenously. During Period 2, subjects were randomized to receive either 20 mg RBP or placebo daily for 13 days beginning on Day 1. On Days 8-10, subjects were given a single oral 200 mg dose of phenytoin administered as before, in addition to continued dosing with either RBP or placebo. On Day 11, 250 mg phenytoin was administered intravenously. There was a 3-day washout interval between Periods 1 and 2.

There were no statistically significant treatment differences ($p>0.07$) observed between the RBP and placebo groups in the changes from Period 1 to Period 2 for any of the PK parameters.

Table VII.30. Mean±SD PK parameters for phenytoin.

PK Parameter	RBP group Period 1 (N=11)	RBP group Period 2 (N=11)	Placebo group Period 1 (N=10)	Placebo group Period 2 (N=10)
AUC_{0-T} (μg*hr/ml)	257±153	250±147	206±90	187±89
Cmax (μg/ml)	10.3±2.0	10.3±1.9	10.2±1.1	9.5±1.5
Tmax (hr)	0.3±0.2	0.4±0.6	0.2±0.1	0.2±0
kel (1/hr)	0.04±0.02	0.04±0.02	0.05±0.01	0.05±0.01
Half-life (hr)	22.7±15.7	22.3±15.2	16.9±6.7	16.8±6.7

Reviewer's Comments:
It is difficult to assess any potential impact of RBP on phenytoin absorption in this study, as PK parameters for phenytoin were determined after **intravenous** administration of this compound. Phenytoin plasma concentrations did not reach therapeutic levels (10-20 μg/ml) in many subjects, therefore, the data may not be clinically relevant. There were also numerous protocol violations during the execution of this study (see Study Synopses in Appendix II for details). In conclusion, due to the issues discussed above, the results of this study provide less than ideal information to enable assessment of a potential drug interaction between rabeprazole and phenytoin.

6. Protocol #A001-113 - **A study of the effect of rabeprazole on the pharmacokinetics of diazepam in healthy male volunteers.**

This was a randomized, single-center, placebo-controlled, blinded, two-way crossover study performed in 20 normal, healthy males. Prior to the start of the treatment periods, each subject received a single 100 mg dose of mephenytoin for assessment of mephenytoin hydroxylation status. During Period 1, subjects received either a single, oral, 20 mg dose of RBP or placebo daily for 35 days. On Day 8, one hour after administration of RBP or placebo, a 0.1 mg/kg dose of diazepam was administered as a 5-minute intravenous infusion. During Period 2, subjects received the alternate treatment (RBP or placebo). Periods 1 and 2 were separated by a 21-day washout interval. Both diazepam and nordiazepam plasma concentrations were assessed in this study.

Two of the subjects were classified as poor metabolizers of mephenytoin and the remaining 17 subjects were extensive metabolizers. There were no statistically significant treatment differences observed for any of the diazepam PK parameters for either the analysis including all

subjects nor the analysis excluding the PMs. Likewise, there were no statistically significant sequence nor period effects observed for either analysis for any of the diazepam PK parameters. Results of the PK calculations and statistical analyses are provided in Table VII.31. below.

Table VII.31. Mean±SD PK parameters for diazepam – all subjects.

PK Parameter	RBP group (N=19)	Placebo (N=19)	Ratios (%) and (90% CI) p-value[a]	
			Untransformed data	Log-transformed Data
$AUC_{0-\infty}$ (ng*hr/ml)	12247±4489	16671±26579	72.5 (13.6;132) 0.429	98.6 (78.6;123.6) 0.913
Cmax (ng/ml)	511.3±281.8	490.5±406.9	105.5 (64.4;147) 0.818	109.9 (88.1;137.1) 0.469
Tmax (hr)	0.5±0.9	0.5±0.9	98.6 0.980	NA
Kel (1/hr)	0.02±0.01	0.02±0.01	100.2 0.981	NA
Half-life (hr)	50.9±26.1	165.6±517.7	29.8 0.311	NA
Cl_{total} (ml/hr)	698±265	721±257	96.4 0.647	NA
Vss (ml)	17722±9864	18739±10774	94.9 0.593	NA
MRT (hr)	30.2±25.9	53.2±121.3	56.2 0.364	NA

[a]p-value for treatment effect from ANOVA analysis

No statistically significant treatment effects were seen for any of the nordiazepam PK parameters when the RBP and placebo treatment periods were compared for all subjects or when the PMs were excluded. There were, however, significant period effects for kel and MRT for both untransformed and log-transformed data when all subjects were analyzed, and when the PMs were excluded from the analysis. The significance of these effects is unknown.

In conclusion, there did not appear to be an interaction between RBP and diazepam when all subjects were analyzed or when the PMs were excluded from the analysis.

7. Protocol #J081-020 - **A study of the effect of E3810 and omeprazole on the pharmacokinetics of intravenous diazepam in Japanese healthy male volunteers.**

As this study was similar to the diazepam study discussed above, it was not reviewed in depth. The reader is referred to the individual Study Synopses in Appendix II for study details.

8. Protocol #J081-028 - **A study of the effect of a single dose of antacid on the pharmacokinetics of E3810 in healthy meal volunteers.**

This was a randomized, open-label, three-way cross-over study to evaluate the effects of a single dose of antacid (Maalox®, 30 ml) on the PKs of RBP (20 mg) in 12 healthy, Japanese, male subjects. RBP was administered without antacid, concomitantly with antacid, and 1 hour after antacid. There was a washout period of 1 week between treatments.

The PK results are provided in Table VII.32 below. In clinical practice, it can be assumed that antacids may be taken concomitantly with RBP for symptom relief. Maalox® was selected

because it is one of the most widely used antacid products. There were no statistically significant differences ($p>0.05$) observed in Cmax, Tmax, AUC_{0-12}, or half-life when RBP was administered alone, concomitantly with Maalox®, or one hour after Maalox® administration. Therefore, it can be concluded that no interaction occurred between RBP and this antacid.

Table VII.32. Mean±SD RBP PK parameters for each treatment group.

Parameter	Without Maalox (N=12)	Concomitant Maalox (N=12)	Maalox 1 hr before RBP (N=12)
AUC_{0-12} (ng*hr/ml)	1020.8±713.0	942.9±604.7	960.1±624.4
Cmax (ng/ml)	516.8±269.5	630.5±321.7	601.3±315.5
Tmax (hr)	3.6±1.1	3.4±1.1	4.0±1.3
Half-life (hr)	1.2±0.7	1.1±0.6	1.1±0.6

Conclusions from Drug Interaction Studies

RBP has two properties which give it the potential to interact with other drugs. It is metabolized by the CYP450 system and could, therefore, compete for metabolism with other compounds. RBP can also significantly increase gastric pH, affecting drugs that are dependent on an acid environment in the stomach for absorption.

Studies examining the co-administration of theophylline, diazepam, and warfarin (all metabolized by CYP450s) did not reveal any interactions. In the clinical trials, antacids were used concomitantly with RBP, however, no interaction between RBP and antacid was observed in the drug interaction study discussed above.

Expected interactions were observed for compounds with pH-dependent absorption. Co-administration of RBP resulted in an approximately 30% decrease in the AUC and Cmax for ketoconazole and a 20-30% increase in the BA of digoxin. Therefore, individual patients may need to be monitored to determine if a dosage adjustment is necessary when such drugs are given concomitantly with RBP.

VIII. PHARMACODYNAMIC STUDIES

There were 10 PD studies submitted to elucidate the PDs of RBP in both Japanese and American/European populations. Eight of these studies were reviewed in depth.

A. Protocols #J081-026 and #L001-B

These studies were not reviewed in depth as the data supported an indication for which approval is not being sought.

B. Japanese Studies

1. Protocol #J081-007 - A comparison of two doses of the proton pump inhibitor, E3810, versus famotidine and pirenzepine using 24 hour monitoring of gastric pH in healthy volunteers.

This was a randomized, open-label, 4-way cross-over study in 8 healthy Japanese volunteers. A comparison of two doses of RBP (daily doses of 10 mg and 20 mg) vs famotidine (40 mg) and pirenzepine (75 mg) given for four consecutive days, was performed using 24-hour gastric pH

monitoring. Results were expressed in terms of pH holding times (proportion of the total measured time during which the pH was maintained above a specified value, expressed as % of time).

It was observed that significant differences existed between 20 mg RBP and basal levels for the entire 24-hour period. However, no significant differences were observed between 10 mg RBP and basal levels. In addition, there were no significant differences found between either the 10 mg or 20 mg RBP doses and basal conditions for any of the four 6-hour intervals. The following table provides a summary of the mean pH holding times at pH 4.

Table VIII.1. Mean pH 4 holding times (%).

	24 hour	07:00-13:00	13:00-19:00	19:00-01:00	01:00-07:00
Basal	41.3	38.0	36.8	46.0	44.4
10 mg RBP	64.7	44.3	78.8	74.5	61.1
20 mg RBP	76.4[a]	58.5	85.9	85.6	75.7
Famotidine	36.4	29.7	25.2	27.4	63.2
Pirenzepine	19.7	17.4	23.8	22.6	15.1

[a] $p \leq 0.05$ vs 24-hour basal based on Tukey's test and Dunnet's t-test

2. Protocol #J081-008 - A study of the effects of the proton pump inhibitor, E3810, on gastric pH - comparison of morning vs. evening dosing regimen using continuous monitoring of gastric pH.

This was an open-label, multi-center, comparative study designed to compare the effects of once daily administration of RBP (20 mg) for 4 consecutive days, in the morning or evening, on intragastric pH using 24-hr continuous monitoring. The study population included 15 patients with gastric ulcer or duodenal ulcer.

Significant ($p \leq 0.001$) extension of the pH 3 holding time was achieved with both modes of RBP administration compared to basal values. The 24-hour pH 3 holding times in the post-breakfast group were 356±262 minutes predose and 1418±37 minutes on Day 4 of dosing. The corresponding times in the post-dinner group were 468±343 minutes and 1304±129 minutes. Likewise, the mean pH 3 holding times for the morning and night-time intervals were significantly greater at Day 4 compared to predose values in both the post-breakfast and post-dinner groups (see Table VIII.2.).

Table VIII.2. Mean±SD pH 3 holding times (minutes).

		Post-breakfast group	Post-dinner group
Predose	08:00 to 20:00	84.0±61.4	215.1±169.6
	20:00 to 08:00	271.9±226.0	252.6±212.1
Day 4	08:00 to 20:00	712.0±14.8[a]	650.0±73.3[b]
	20:00 to 08:00	706.0±37.0[a]	653.7±76.7[b]

[a] $p<0.001$ vs corresponding times predose
[b] $p<0.001$ vs corresponding times predose

Gastric pH levels in the post-breakfast group remained at a pH value of approximately 2 throughout the 24-hour pre-dosing period. By Day 4 the gastric pH level was above 5 for most of the 24-hour period. Similar results were observed for the post-dinner group.

Mean serum gastrin levels increased for both GU and DU patients, although the increases were not statistically significant. Serum pepsinogen levels were higher than the normal range for patients with both types of ulcers, pre- and post-dosing with RBP. In addition, a significant elevation ($p \leq 0.001$) of serum pepsinogen level was observed in the DU patients after RBP administration.

It was concluded that either a morning or evening dosing regimen would be equally effective for the treatment of peptic ulcers.

3. Protocol #J081-018 - **A study of the effects of the proton pump inhibitor, E3810, on gastric juice secretion – basal and gastrin-stimulated gastric acid and pepsin secretion in healthy volunteers.**

This was an open-label, single-center, pharmacodynamic study in 5 healthy Japanese adults who were administered single daily 20 mg doses of RBP for 7 days. Gastric juice samples were obtained pre-dose, 6 hours after the initial dose (Day 1), 6 hours after the final dose (Day 7), and 24 hours after the final dose (Day 8). Gastric juice was collected for a time period of 2.5 hours during each monitoring day. The first 3 samples (30 minutes) were basal secretion, followed by amogastrin-stimulated (4μg/kg intramuscular) secretion during the next 120 minutes.

The following table provides the PD parameters for all treatment and pH monitoring periods. In addition to the parameters listed below, gastric juice pH exhibited marked increases on Days 1 and 7 during both basal and stimulated secretion (data not shown), while on Day 8 a decline was observed, also indicating a partial recovery of gastric acid secretion.

Table VIII.3. Decreases (%) in gastric juice, acid, and pepsin secretions (means±SD).

Secretion		Day 1	Day 7	Day 8
Gastric Juice	Basal	72.1±18.3[a]	75.9±14.0[a]	57.9±20.2
	1 hr stimulation	77.6±17.3[b]	89.0±7.1[b]	68.8±3.2[b]
	2 hr stimulation	76.7±16.0[b]	87.2±6.9[b]	69.1±3.3[b]
Gastric Acid	Basal	88.1±10.2	94.7±7.7	87.7±14.0
	1 hr stimulation	88.7±14.5[b]	99.0±1.6[b]	88.6±3.1[b]
	2 hr stimulation	88.1±13.8[b]	98.6±1.3[b]	89.1±3.3[b]
Pepsin	Basal	82.0±24.8[a]	85.3±18.2[a]	88.3±12.7[a]
	1 hr stimulation	64.3±32.7[a]	88.4±20.8[c]	51.0±6.4[c]
	2 hr stimulation	61.0±32.4[a]	87.2±18.9[c]	55.8±8.0[c]

[a] $p \leq 0.05$ vs Day 0
[b] $p \leq 0.001$ vs Day 0
[c] $p \leq 0.01$ vs Day 0

RBP markedly inhibited both basal and stimulated gastric juice, gastric acid, and pepsin secretion, beginning with the initial dose (Day 1). However, the inhibition of gastric acid secretion was not statistically significant under clinically relevant basal conditions. This may have been due to the gastric juice sampling method used; i.e., had gastric juice been sampled more frequently or for a longer time span after RBP administration, instead of for just 2.5 hours beginning at 6 hours post-dose, the reductions in gastric acid secretion may have reached statistical significance. These findings also suggest that gastric acid secretion begins to recover by 24 hours after a RBP dose.

4. Protocol #J081-019 - A comparison of the effects of 7 days dosing of the proton pump inhibitors, E3810 or omeprazole, on intragastric pH and serum and urinary gastrin levels in healthy volunteers.

This was a randomized, open-label, cross-over study to compare the effect of 7 days of dosing with RBP (20 mg) and OMP (20 mg) on intragastric pH, and serum and urinary gastrin levels in 8 healthy Japanese volunteers.

The percent increases in pH 3 holding times from Day 0 to Days 6-7 were greater during RBP administration than during OMP administration, however, the differences between the two drugs were not statistically significant due to large fluctuations in the data. Table VIII.4. displays the mean changes in gastric pH 3 holding times for the 24-hour monitoring period and for each of the individual 6-hour time intervals.

Table VIII.4. Changes (minutes) in pH 3 holding times (means±SD).

		RBP (N=7)	OMP (N=8)
24-hour period	Day 0	331±288	360±277
	Days 6-7	1175±174 *(255%)*[a]	1103±329 *(206%)*[a]
	Day 8	849±277 *(28%)*[b]	816±272 *(26%)*[b]
08:00 to 14:00	Day 0	86±68	122±79
	Days 6-7	298±39[a]	283±68[a]
	Day 8	267±72[b]	253±27[b]
14:00 to 20:00	Day 0	92±88	83±83
	Days 6-7	349±15[a]	318±64[a]
	Day 8	232±108[b]	215±76[b]
20:00 to 02:00	Day 0	45±37	69±66
	Days 6-7	275±75[a]	232±109[a]
	Day 8	150±87[b]	133±85[b]
02:00 to 08:00	Day 0	108±154	86±98
	Days 6-7	253±124[a]	270±129[a]
	Day 8	200±156[b]	214±141[b]

[a]the % increase in 24-hour pH 3 holding time compared to Day 0
[b]the % decrease in 24-hour pH 3 holding time compared to Days 6-7

On Day 8, serum gastrin levels were statistically significantly elevated compared to Day 0 for both drugs. On Day 9, serum gastrin levels for both drugs had decreased to levels, which were close to and not significantly different from, the Day 0 levels. Likewise, urinary gastrin excretion after drug administration was statistically significantly higher than before administration for both drugs (data not shown). However, there were no significant differences between RBP and OMP for either the urinary or serum gastrin data. Table VIII.5. displays the mean serum gastrin levels for each group.

Table VIII.5. Mean±SD serum gastrin[a] levels (pg/ml).

	RBP group	OMP group
Day 0 (N=8)	65.5±21.7	73.4±34.0
Day 8 (N=8)	104.9±39.4	127.3±63.7
Day 9 (N=7)	85.1±33.5	78.3±33.1

[a]Normal range: 42-200 pg/ml.

In conclusion, administration of both RBP and OMP for 7 days resulted in significant gastric acid suppression and elevations in serum and urinary gastrin levels. However, there were no statistically significant differences between the two drugs with respect to any of the parameters evaluated in this study.

Reviewer's Comments with regards to the Japanese PD Studies:
In general, very little information was provided with these study reports. For example, no raw individual data was provided for any of the PD measurements, only the summarized results and mean data. In addition, no information was provided regarding subject demographics, clinical laboratory values, or adverse events. Although planned in the study protocol, no PK results were reported. In view of these issues, the bulk of the data presented from these four studies should be interpreted as qualitative, rather than quantitative.

C. American/European Studies

1. Protocol #E044-106 - A trial to assess the effect of E3810 on endocrine function and gastric secretory function in young healthy male Caucasian subjects.

This was a single center, double-blind, randomized, placebo-controlled, crossover study to determine the effect of 20 mg RBP, compared to placebo, on endocrine and gastric secretory function in 12 healthy, male, Caucasian volunteers during a 14-day treatment period.

Primary Endocrine Function
Comparison of the serum testosterone levels after 13 days of RBP treatment and 13 days of placebo showed no significant difference (p=0.14, ANOVA). The means and standard deviations were 6.2±1.4, 6.2±1.5 and 6.9±1.6 ng/mL for baseline, Day 13 of RBP treatment, and Day 13 of placebo, respectively. All of these values were within normal limits (2.8-9.0 ng/ml).

There were no significant differences in the circadian cortisol profile after 13 days of dosing with either RBP or placebo (Table VIII.6.). The baseline values, which were not included in the statistical analyses, were 16.2±3.3, 11.6±4.1, 5.2±4.4, and 3.7±2.0 μg/dL for 8 AM, 2 PM, 8 PM, and 2 AM, respectively. The baseline values were similar to the Day 13 values.

Table VIII.6. Circadian cortisol profile (mean±SD, μg/dL)

Sampling Time Days 13 – 14	RBP 20 mg (N=12)	Placebo (N=12)	p-value
8 AM	15.1 ± 4.6	15.2 ± 6.3	0.922
2 PM	9.3 ± 3.8	9.8 ± 4.1	0.765
8 PM	2.7 ± 1.9	5.4 ± 6.4	0.161
2 AM	3.1 ± 2.8	6.1 ± 4.5	0.063
8 AM	15.1 ± 3.1	14.4 ± 2.9	0.591

Other Endocrine Function
Except for aldosterone, there were no statistically significant differences in the analyses of other measures of endocrine function after 13 days of RBP treatment compared to placebo. These other parameters included measures for thyroid and parathyroid function, glucose control, corticosteroid synthesis and reproductive hormones. The mean and standard deviation values for aldosterone were 83.9±34.4 pg/mL after RBP and 108.6±35.4 pg/mL after placebo (p = 0.02). However, this finding is unlikely to be clinically significant because there were no other changes in related parameters and the baseline value for aldosterone was 88.3±24.8 pg/mL, which is

closer to the value after RBP treatment than the value after placebo treatment. In addition, all mean aldosterone values remained well within normal limits (40-310 pg/ml). Thus, the analysis of other measures of endocrine function did not reveal any clinically relevant effect of RBP.

Pharmacodynamics

For Days 7 and 14 of treatment and the first two days post-treatment, the intragastric acidity was significantly lower for RBP treatment than placebo treatment for the 24-hr period and all 4 meal-related intervals. After 14 days of dosing, RBP reduced the 24-hour integrated intragastric acidity by 87% compared to placebo treatment. Although still significantly less than placebo, the intragastric acidity after RBP treatment on Days 15 and 16 was higher compared to Days 7 and 14, indicating a partial recovery of gastric acid secretion. Mean intragastric acidity values are provided in Table VIII.7. below.

Table VIII.7. Summary of Mean±SD Intragastric Acidity (mmol/L/hr)

Study Day	Time Interval (hr)	Placebo	20 mg RBP	p-value[a]
Day 7	Morning (08-13)	76.2±52.3	14.5±30.5	<0.001
	Afternoon (13-19)	110.7±76.1	2.5±4.2	<0.001
	Evening (19-22)	54.4±42.4	4.1±7.8	<0.001
	Night (22-08)	262.1±136.9	50.3±79.6	<0.001
	24-hour (08-08)	503.4±245.5	71.4±92.2	<0.001
Day 14	Morning (08-13)	38.6±53.4	0.4±0.5	<0.001
	Afternoon (13-19)	76.5±121.6	2.5±4.5	<0.001
	Evening (19-22)	70.8±58.3	12.8±20.7	<0.001
	Night (22-08)	157.0±153.7	28.0±34.0	<0.001
	24-hour (08-08)	342.8±352.2	43.7±43.1	<0.001
Day 15	Morning (08-13)	43.3±40.6	18.7±21.2	<0.001
	Afternoon (13-19)	110.9±126.4	36.9±35.7	<0.001
	Evening (19-22)	124.6±106.9	41.8±36.2	<0.001
	Night (22-08)	222.0±214.3	28.7±35.4	<0.001
	24-hour (08-08)	500.8±419.4	126.0±106.5	<0.001
Day 16	Morning (08-13)	37.9±21.6	21.7±16.5	<0.001
	Afternoon (13-19)	52.4±48.8	26.7±22.8	<0.001
	Evening (19-22)	85.6±73.5	44.4±37.5	<0.001
	Night (22-08)	203.2±175.3	53.7±50.9	<0.001
	24-hour (08-08)	379.1±255.5	146.5±100.2	<0.001

[a]p-value for treatment obtained from ANOVA with effects for sequence, subjects within sequence, period, and treatment

In conclusion, treatment with RBP did not result in any clinically or statistically (except for aldosterone) significant effects on serum testosterone levels, circadian serum cortisol profiles, ACTH-stimulated serum cortisol levels, or 17 other measures of endocrine function when compared with placebo treatment. The changes observed for aldosterone are unlikely to be of clinical significance. RBP treatment statistically significantly decreased intragastric acidity compared with placebo during all of the time intervals on all of the Days examined in this study.

2. Protocol #E044-107 - **A trial to assess the effect of seven-day dosing of rabeprazole on 24-hour intragastric acidity and plasma gastrin concentrations in young, healthy, male subjects.**

This was a single-center, double-blind, randomized, placebo-controlled, four-period crossover study in 24 healthy, male volunteers to determine the effect of RBP at three dose levels (10 mg,