D. Study #A001-114

This was a randomized, two-treatment, two-period, two-way crossover study in 28 healthy, American, male and female volunteers to evaluate the BE of 1x20 mg RBP tablet manufactured at the Kawashima site (biobatch) versus 1x20 mg RBP tablet manufactured at the Misato site (to-be-marketed batch). This is the pivotal BE study for this NDA. The mean PK parameters from the data analysis are provided in Table IV.4.

Table IV.4. Mean±SD (%CV) PK parameters for all evaluable subjects.

Parameter	Kawashima Lot (N=24)	Misato Lot (N=24)	Ratios (%) and 90% CI* Log-transformed data (Misato/Kawashima)
AUC_{0-24} (ng*hr/ml)	860.9±476.9 (55%)	856.4±523.2 (61%)	Ratio=99.6 (87.0;109.6)
$AUC_{0-\infty}$ (ng*hr/ml)	886.2±474.7 (54%)	885.7±526.2 (59%)	Ratio=99.7 (88.0;109.0)
Cmax (ng/ml)	583.2±210.3 (36%)	557.0±338.5 (61%)	Ratio=83.8 (68.5;102.6)
Tmax (hr)	3.6±1.0 (28%)	4.3±1.5 (35%)	Not applicable
Kel (hr)	0.96±0.39 (41%)	0.94±0.41 (44%)	Not applicable
Half-life (hr)	0.9±0.5 (56%)	1.0±0.7 (70%)	Not applicable

*CI are based on least square means.

The mean AUC_{0-T} and $AUC_{0-\infty}$ data were equivalent based on the Two One-Sided Tests Procedure for the 90% CI range of 80-125% using log-transformed data. However, the Cmax was not BE based on the same criteria, with the Misato product resulting in approximately 5% lower mean values (untransformed data). No significant effects due to sequence or period were observed for the analyses of Cmax. Likewise, there were no sequence, period, or treatment effects observed for kel or half-life. Although the sequence effect was not significant, there was a suggestion of a period effect for AUC_{0-T} and $AUC_{0-\infty}$ ($p=0.070$ and $p=0.054$, respectively). A significant treatment effect was seen for tmax ($p=0.01$), but no sequence nor period effects were evident.

E. Study #A001-118

The purpose of this study was to evaluate the BE of the 10 mg RBP tablets manufactured at the Kawashima and Misato sites, however, since the firm will not be marketing a 10 mg tablet, this study was not reviewed.

Table IV.5. provides information for each of the strengths and formulations of RBP used in all pivotal clinical trials and the PK studies included in this NDA.

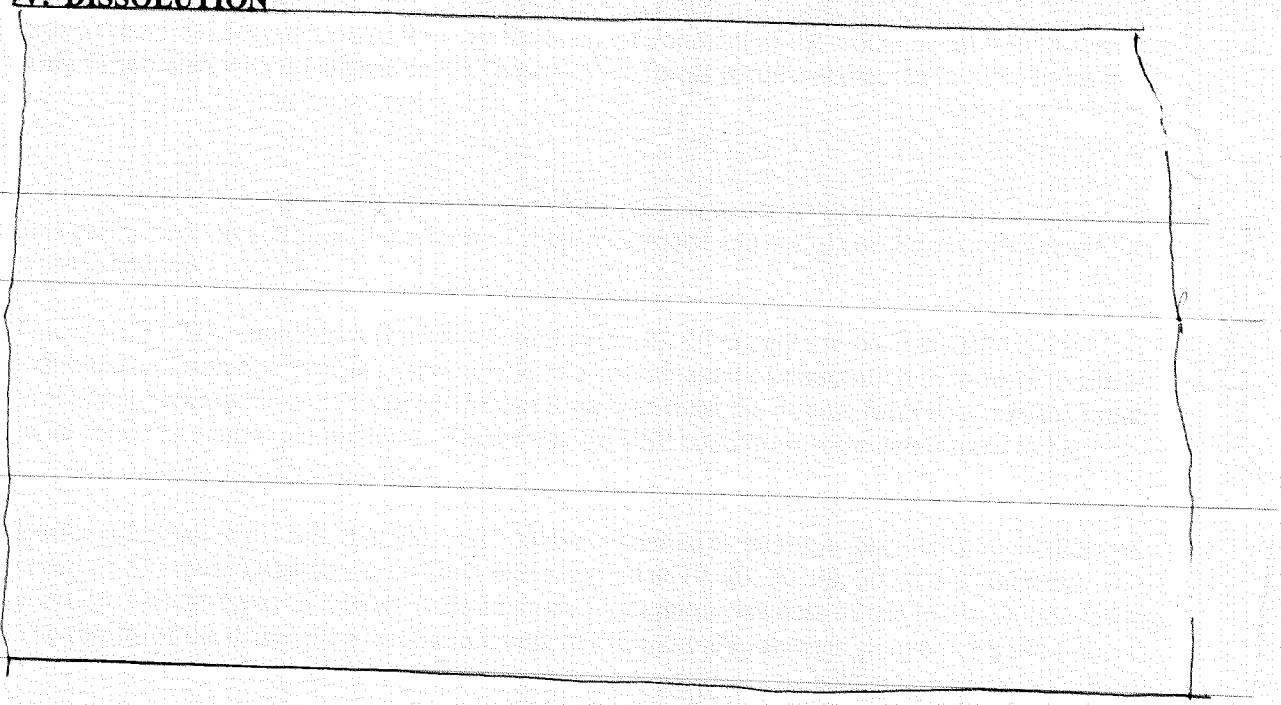
Table IV.5. Formulations of RBP used in the PK studies and the clinical trials.

Formulation Number	Strength (mg)	BE Study Protocol Number	PK Study Protocol Number	Pivotal Clinical Trial Protocol Number
0002BC	1	Not evaluated	J081-001	
0005	5	J081-010[4]	Not reviewed	None
0003A	10	J081-010, J081-009	A001-001, A001-002	None
0003AC	10	Not evaluated	J081-007, J081-008	None
0003BC	10	Not evaluated	J081-001, J081-003, J081-004	None
0006	10	Not evaluated	E044-107	NRRK, NRRI
0008	10	A001-109	None	NRRK
0004[1]	20	J081-009	L001-A, E044-106, J081-018, J081-019, J081-020, J081-027, J081-028	All
0007[1,2]	20	A001-109, A001-114	All others not listed	NRRK
061457[1,2]	20	A001-114	None	None
061640[3]	10	Not reviewed	Not reviewed	None

[1]These formulations all contain the same components in equal quantities.
[2]Batches used in the pivotal BE study; ie., #0007 was a clinical batch and #061457 was a production-scale batch.
[3]This was an intended to-be-marketed strength.
[4]Shaded areas indicate studies for which the formulations were not bioequivalent.

The the components and their quantities for the 10 mg formulations, #0006 and #0008, were the same. Likewise, the 20 mg formulations, #0004 and #0007, were the same. Therefore, based on the information and the results of the BE studies presented above, the following formulations can be considered to be BE: 2x10 mg of #0006, 2x10 mg of #0008, 1x20 mg of #0004, and 1x20 mg of #0007. Thus, there are no BE links between formulations #0002BC, #0005, #0003A, #0003AC, or #0003BC to the formulations that are considered to be BE.

V. DISSOLUTION



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VII. BIOAVAILABILITY AND PHARMACOKINETIC STUDIES

As stated previously, the PK studies were done in Europe, Japan, and the United States. All protocol numbers which begin with #J081 are studies which were performed in Japan, while the remainder were performed in either Europe or the United States. Detailed synopses of every study, including methodology, can be located in Appendix II.

A. Mass Balance Study:

1. Protocol #E044-111 - Excretion balance and pharmacokinetics at steady state after single dose oral intake of ^{14}C-E3810 in healthy volunteers.

This study was an open-label PK and mass-balance study in 6 healthy males, with administration of radiolabeled RBP (20 mg) after attainment of steady state with unlabelled doses (20 mg for 7 days). The recovery of ^{14}C-radioactivity, as well as PK parameters derived from plasma ^{14}C-radioactivity curves, are summarized as follows:

Table VII.1. ^{14}C-radioactivity PK parameters.

PK Parameter	Means±SD (N=6)	Range
Cmax (ng eq/ml)	1080±215	829-1387
Tmax (hr)	0.25[1]	0.25-0.50
Kel (hr^{-1})	0.058±0.012	0.036-0.066
$t_{½}$ (hr)	12.6±3.4	10.5-19.3
C_{24hr} (ng eq/ml)	13.0±2.91	9.63-17.3
C_{24hr}/Cmax (%)	1.20±0.06[1]	1.15-1.28
AUC_{0-24} (ng eq*hr/ml)	2712±705	1930-3711
$AUC_{0-\infty}$ (ng eq*hr/ml)	2950±739	2100-3983
A_{urine} (%)	90.0±1.7	87.8-92.6
A_{feces} (%)	9.8±1.8	8.0-12.7
A_{total} (%)	99.8±0.7	98.7-100.7

[1]Median values.

From this data it can be observed that the excretion of the administered radioactivity was complete and rapid. The total recovery was >98% in all cases, with more than 90% excreted within the first 48 hours. Cumulative excretion in the urine and feces was approximately 90% and 10%, respectively.

With respect to the metabolic profile for RBP, the results indicated that the systemic exposure to most of the metabolites was minimal; i.e., S, DM, DMTE, and MA. Parent RBP was the primary drug-related component detected in plasma during early timepoints after dosing, and was replaced at later times by the TE and TEC metabolites. TEC declined in parallel to the TE, suggesting that the PKs of TEC were formation-rate limited. This, coupled with the clearance of TEC in urine and feces, should minimize the systemic exposure to all of the known metabolites of RBP in humans.

Recovery of ^{14}C-radioactivity from urine and feces was nearly complete. The predominant

metabolites excreted into the urine were the TEC and MA derivatives of the parent compound. Their recoveries accounted for approximately 30% and 25%, respectively, of the administered dose, and together they represented about 70% of the total radioactivity excreted into the urine within 24 hours. The relatively low fecal excretion suggests that elimination of RBP or its metabolites by the biliary route was minor.

B. In Vitro Metabolism Study:

1. Protocol #A46:ADME – Interaction of Human Liver Cytochrome P450 with 307640 *In Vitro*

The interactions *in vitro* of 307640 (RBP) with CYP450 were studied using human liver microsomes, specific inhibitors of the CYP450s, and cDNA-expressed enzymes. The kinetics of formation of the two major oxidative metabolites, DM-RBP and RBP-S, were determined using human liver microsomal samples at RBP substrate concentrations of 2.5-500 uM (<1-7 μM observed in plasma after oral doses of 10-80 mg RBP). The kinetic data indicated that high and low affinity sites were present for the production of both metabolites of RBP. The $km_{apparent}$ and $Vmax_{apparent}$ for DM-RBP formation for the high affinity site were 18.8±4.4 μM and 402±52 pmol product/min/mg protein. The high affinity site $km_{apparent}$ and $Vmax_{apparent}$ for RBP-S formation was 4.4±2.1 μM and 81.8±18 pmol product/min/mg protein. The rates of DM-RBP and RBP-S formation by the high affinity site were determined using 14 human liver microsomal samples characterized for CYP450 marker catalytic activities and immunoquantified levels of the CYP450. Rates of formation of DM-RBP significantly correlated with the immunoquantified levels of CYP 2C19 and the ability of the microsomes to 4'-hydroxylate S-mephenytoin. RBP-S formation significantly correlated with the immunoquantified levels of CYP 3A and the ability of the microsomes to 1'-hydroxylate midazolam. Inhibition studies and use of expressed CYP450 systems confirmed the correlation data demonstrating that CYP 2C19 catalyzed the formation of DM-RBP and CYP 3A catalyzed RBP-S formation. Further, RBP competitively inhibited S-mephenytoin 4'-hydroxylation and midazolam 1'-hydroxylation, as did the structurally related compound, omeprazole. For the inhibition of S-mephenytoin 4'-hydroxylation and midazolam 1'-hydroxylation, RBP had higher $ki_{apparent}$ values than that of omeprazole (9.2±1.0 μM vs 4.1±0.4 μM for S-mephenytoin 4'-hydroxylation, and 59.4±6.0 μM vs 43.6±5.7 μM for midazolam 1'-hydroxylation for RBP and omeprazole, respectively). These studies demonstrate that the high affinity enzymes which catalyze the formation of the DM and S metabolites of RBP are, respectively, CYP 2C19 and CYP 3A. In addition, the inhibition data suggest that RBP has less potential to inhibit the metabolism of CYP 2C19 substrates compared to omeprazole, and that RBP and omeprazole have a similarly low potential to inhibit the metabolism of CYP 3A substrates. The proposed metabolic pathway for RBP is displayed in Appendix I as Figure 5.

RBP is extensively biotransformed to primary and secondary metabolites in mice, rats, dogs, as well as humans. In all species, the TE is formed via reduction from RBP in the intestine and is absorbed along with RBP. The TE is also formed systemically after absorption. RBP is also extensively metabolized by the liver to the other metabolites illustrated above. In humans, the primary metabolite is the TE, which is then oxidized (via DMTE) to the TEC. Very low levels of the S are present, and the DM metabolite has only been detected in a few plasma samples from a few subjects in human plasma. As the DM metabolite retains the chiral sulfoxide group, which is essential for binding to the target enzyme, it could potentially contribute to pharmacologic activity. However, since DM is not present in human plasma to any appreciable extent, its contribution to the pharmacologic activity of RBP is likely to be of little significance. The pharmacologic activities for RBP and its metabolites are summarized below.

Table VII.2. Pharmacologic activity for RBP and its metabolites.

Compound	Pharmacologic Activity (IC_{50} for H^+, K^+-ATPase Inhibition)
Rabeprazole	0.20 uM
Thioether	≥ 100 uM
Sulfone	> 100 uM
Desmethyl	0.29 uM
Desmethyl Thioether	>100 uM
Mercapturic Acid	>100 uM
Thioether Carboxylic Acid	>100 uM

C. Single-dose Studies:

1. Protocol #A001-001 – An ascending, single-dose safety and tolerance study of an oral formulation of E3810 in healthy male volunteers.

This was an ascending, single-dose, sequential-group, placebo-controlled study performed in 40 healthy males. In this preliminary study, plasma concentrations of RBP were measured following single doses of 10 mg, 20 mg, 30 mg, and 40 mg. Ten volunteers were recruited for each group; 8 received active drug and 2 placebo. PK parameters derived from this study are presented below.

Table VII.3. Mean±SD PK parameters for RBP.

PK Parameter	Dose Group			
	10 mg (N=8)	20 mg (N=8)	30 mg (N=8)	40 mg (N=8)
Cmax (ng/ml)	184±135	294±101	615±228	800±536
Tmax (hr)	2.9±0.6	2.9±0.4	2.9±0.4	2.8±0.9
$T_{½}$ (hr)	0.73±0.16	0.70*±0.16	0.86±0.29	1.01±0.36
Cl/F (ml/min/kg)	9.5±4.6	9.6±5.9	7.6±4.9	7.9±5.3
$AUC_{0\text{-}24hr}$ (ng*hr/ml)	315±211	545±215	1182±536	1554±1023

*Excluding subject 17 with $t_{½}$ =4.75 hrs

Although increasing trends were observed for AUC and Cmax with higher doses, there were no statistically significant differences between treatment groups when adjusted for a 10 mg dose ($p>0.05$). Similar trends were observed when the data were weight-normalized. Furthermore, when oral clearance was plotted and regressed as a function of RBP dose, the slope was not statistically significantly different from zero, indicating dose-independence for this parameter. This data indicates that the PKs of RBP are linear between doses of 10 to 40 mg.

Table VII.4. Mean dose-normalized PK parameters for RBP (adjusted to 10 mg dose).

PK Parameter	Dose Group			
	10 mg (N=8)	20 mg (N=8)	30 mg (N=8)	40 mg (N=8)
Cmax (ng/ml)	184	147	205	200
$AUC_{0\text{-}24hr}$ (ng*hr/ml)	315	273	394	389

2. Protocol #J081-001 – **A single, ascending dose study to evaluate the safety, tolerance, and pharmacokinetic profiles of E3810 in healthy male volunteers.**

This placebo-controlled, double-blind, ascending single oral dose study was conducted to evaluate the PKs of RBP and its metabolites in plasma and urine at doses of 1, 3, 10, 20, 40, and 80 mg in 18 healthy, Japanese male volunteers. The subjects were divided into two groups of nine: Group 1 received either 1, 10, and 40 mg RBP or placebo, while Group 2 received either 3, 20 and 80 mg RBP or placebo, with a two-week washout period between treatments.

The PK results are provided in the tables below. Due to insufficient reliable plasma concentration data, no data analysis was performed for RBP and its metabolites after either the 1 mg or 3 mg dose. For all other doses, N=6 unless indicated otherwise.

Table VII.5. Mean±SD PK parameters for RBP.

	10 mg	20 mg	40 mg[2]	80 mg
Cmax (ng/ml)	247±59	406±156	1,351±453	2,499±618
Tmax (hr)	3.8±1.3	3.1±0.4	2.9±0.5	3.3±0.9
AUC_{0-t}(ng*hr/ml)	423±56	788±438	2,128±607	4,988±1,934
$AUC_{0-\infty}$(ng*hr/ml)	440±59	809±456	2,153±628	5,212±2,158
Half-life (hr)[1]	0.85±0.09	1.02±0.39	1.06±0.09	1.21±0.32
Cl/F (ml/min/kg)	6.46±1.07	8.4±5.95	5.71±2.74	4.37±1.79

[1]Determined from the terminal 5 points.
[2]n=4 (2 subjects excluded from data analysis due to low plasma levels)

Although there was a trend for greater than proportional increases in $AUC_{0-\infty}$ at higher doses, the values did not reach statistical significance. Likewise, half-life values tended to increase while Cl/F values tended to decrease following higher doses. Again, these did not reach statistical significance. Furthermore, when oral clearance was plotted and regressed as a function of RBP dose, the slope was not statistically significantly different from zero, indicating dose-independence for this parameter. Results of dose-normalized values (based on a 10 mg dose) for RBP AUC and Cmax values are provided in Table VII.6.

Table VII.6. Mean dose-normalized PK parameters for RBP (adjusted to 10 mg dose).

	10 mg	20 mg	40 mg[1]	80 mg
Cmax (ng/ml)	247	203	338	312
$AUC_{0-\infty}$(ng*hr/ml)	440	405	538	652

[1]n=4

DM and DMTE could not be detected in the plasma of any subject. The sulfone metabolite appeared in limited quantities and was only detected in the plasma of every individual after the 80 mg dose. The half-life of the S was similar to that of RBP, indicating formation rate-limited elimination.

Table VII.7. Mean±SD Sulfone PK pararmeters.

	10 mg[1]	20 mg	40 mg	80 mg
Cmax (ng/ml)	ND	22±20[2]	71±28[2]	157±62
tmax (hr)	ND	3.4±0.6[2]	2.9±0.5[2]	3.3±0.9
AUC_{0-t}(ng*hr/ml)	ND	28±47[2]	89±50[2]	341±223
$AUC_{0-\infty}$(ng*hr/ml)	ND	109±134[2]	162±64[2]	387±238
Half-life (hr)	ND	ND[3]	0.93±0.29[4,5]	1.17±0.49[4]

[1]Could not be calculated as all data were <LOQ.
[2]n=4 (some subjects did not provide enough data for analysis)
[3]Not determined as <50% data obtained.
[4]Determined from terminal 3 points.
[5]N=3.

The TE was the primary metabolite of RBP detected in plasma. Its half-life was longer than that of RBP. Furthermore, the mean values provided for TE half-life in the table below may be underestimated, as plasma sampling did not include much of the terminal elimination phase (AUC_{0-t} contributed only 54-74% of the $AUC_{0-\infty}$ after dosing for all treatments). Plasma concentrations of TE exceeded that of the parent compound by about 6 hours post-dose.

Table VII.8. Mean±SD Thioether PK parameters.

	10 mg	20 mg	40 mg[1]	80 mg
Cmax (ng/ml)	51±26	73±40	193±40	419±162
tmax (hr)	5.0±1.1	4.3±0.8	4.3±0.7	4.9±0.8
AUC_{0-t} (ng*hr/ml)	164±139	256±191	789±155	1,763±759
$AUC_{0-\infty}$ (ng*hr/ml)	302±177	378±221	1,069±240	2,998±1,923
Half-life (hr)[2]	3.15±1.10	2.77±0.75	2.95±1.18	3.53±1.60

[1]n=4 (some subjects did not provide enough data for analysis)
[2]Determined from terminal 4 points.

TEC was the primary metabolite found in urine; cumulative excreted amounts of unconjugated TEC, TEC glucuronide, and total TEC into the urine after RBP dosing are provided in Table VII.9. (The difference between the urine concentration of TEC without and with β-glucuronidase incubation was calculated to be the amount of TEC glucuronide present.)

Table VII.9. Cumulative excretion of TEC in the urine.

Cumulative Excretion over 72 hours (% of administered RBP dose)			
	Unconjugated TEC	TEC glucuronide	Total TEC
10 mg dose	22.8±5.1%	10.2±4.5%	33.0±2.3%
20 mg dose	19.1±4.1%	10.8±2.3%	29.9±4.4%
40 mg dose	18.6±1.9%	11.1±0.4%	29.7±1.5%
80 mg dose	21.4±5.7%	8.4±1.7%	29.8±6.7%

In conclusion, the PKs of RBP were roughly linear following single oral doses of 10 to 80 mg, however, a trend was observed for greater than proportional kinetics at higher doses. The S and TE metabolites were observed in plasma at most doses. Based on half-life values and corresponding plasma concentration vs time profiles, the elimination of the S metabolite appears to be formation rate-limited while that of the TE appears to be elimination rate-limited. Only the TEC and TEC glucuronide could be detected in urine in appreciable quantities; their excretion

was not dose-dependent.

3. Protocol #J081-002 – A placebo-controlled, single oral dose, crossover study to evaluate the safety and pharmacodynamics of E3810 in healthy male volunteers.

Since the information contained in this study report was available from studies that were better designed and well-controlled, this study was not reviewed in depth.

D. Multiple-dose Studies:

1. Protocol #A001-002 – An ascending, multiple-dose safety and tolerance study of an oral formulation of E3810 in healthy male volunteers.

This was a double-blind, randomized, placebo-controlled, sequential-group study to assess the safety, PKs, and PDs (intragastric pH and plasma gastrin) of ascending multiple oral doses of RBP. Doses of 10 mg, 20 mg, and 40 mg RBP were administered to 25 healthy male volunteers. Sequential groups of eight volunteers (6 active, 2 placebo) received daily doses of study medication for 14 days. The PK results are provided in table VII.10.

Table VII.10. Mean±SD PK parameters for RBP.

	Dose								
	10 mg (N=6)			20 mg (N=7)			40 mg (N=6)		
PK parameter	*Day 1*	*Day 5*	*Day 14*	*Day 1*	*Day 5*	*Day 14*	*Day 1*	*Day 5*	*Day 14*
AUC_{0-t} (ng*hr/ml)	247± 198	326± 154	283± 180	407± 162	435± 260	684± 489	1302± 458	1388± 590	1505± 523
$AUC_{0-\infty}$ (ng*hr/ml)	247± 198	328± 158	283± 180	408± 164	435± 260	684± 489	1310± 458	1389± 591	1508± 527
Cmax (ng/ml)	153± 110	215± 72	202± 126	238± 116	353± 184	402± 319	775± 296	851± 507	960± 462
Tmax (hr)	5.83± 3.37	3.42± 3.37	3.25± 1.33	2.33± 0.98	2.67± 1.72	5.00± 3.79	3.42± 2.06	2.08± 0.74	2.58± 1.24
Half-life (hr)	0.68± 0.21	0.64± 0.17	0.69± 0.23	0.95± 0.51	1.15± 0.39	0.77± 0.17	1.12± 0.43	1.14± 0.33	0.97± 0.30
Cl/F (L/hr/kg)	0.73± 0.49	0.52± 0.25	0.67± 0.40	0.74± 0.27	0.92± 0.67	0.45± 0.33	0.45± 0.18	0.46± 0.21	0.40± 0.15
Vd (L/kg)	0.76± 0.73	0.47± 0.26	0.70± 0.60	0.94± 0.47	1.62± 1.34	0.49± 0.40	0.65± 0.17	0.74± 0.38	0.53± 0.19

Following absorption, RBP was rapidly eliminated, with plasma concentrations below the analytical assay LOQ by 12 hours post-dose. Although there appeared to be a trend for $AUC_{0-\infty}$ to increase with higher doses, the differences can most likely be attributed to the high intersubject variability at lower doses and the sensitivity limits of the RBP assay at the plasma concentrations observed after the 10 mg dose. There was no consistent effect of dose on Cmax or Tmax. Mean half-life increased with higher doses, while CL/F decreased. However, when oral clearance was plotted and regressed as a function of RBP dose for Days 1, 5, and 14, the slope was not statistically significantly different from zero, indicating dose-independence for this parameter. In conclusion, the PKs of RBP at steady-state appeared to be slightly non-linear over the dose range from 10 to 40 mg, however, with the exception of Cl/F, the sponsor did not perform any formal

statistical analysis of the differences between treatment groups.

Dose-adjusted values for $AUC_{0-\infty}$ and Cmax are provided below. There was also a trend for a time-dependent increase in PK parameters within the 20 and 40 mg dosage groups, however, these differences did not achieve statistical significance according to the sponsor (statistical data not provided).

Table VII.11. Mean dose-adjusted PK parameters (adjusted to 10 mg dose).

	$AUC_{0-\infty}$ (ng*hr/ml)			Cmax (ng/ml)		
	10 mg	*20 mg*	*40 mg*	*10 mg*	*20 mg*	*40 mg*
Day 1	247	204	328	153	119	194
Day 5	328	217	347	215	177	213
Day 14	283	342	377	202	201	240

Pharmacodynamics

There were dose-related increases in the pharmacological response to RBP as measured by mean 24-hour intragastric pH, mean nocturnal pH, and percent of time that 24-hour and nocturnal pH≥3. The increases achieved statistical significance ($p>0.05$) for all three RBP treatment regimens when compared to placebo. The mean 24-hour intragastric pH parameters are displayed in Table VII.12.

Table VII.12. Mean Intragastric pH Parameters

Parameter	Timepoint	Placebo	10 mg RBP	20 mg RBP	40 mg RBP
Mean 24-hr pH	Day 1	1.68	2.39	3.06	4.04
%time pH≥3		15.26	29.17	48.09	67.78
Mean 24-hr pH	Day 14	1.42	3.94	3.99	4.74
%time pH≥3		10.05	66.58	65.15	80.85

The 24-hr values for mean pH and % of time that pH ≥ 3 were similar for Days 5 (data not shown) and 14, indicating that overall, the pharmacological response had reached steady state by Day 5. Upon termination of RBP treatment (Day 15), mean values for all dose groups for 24-hr pH had decreased to approximately 67% of Day 14 values, and those for % of time pH≥3 to 55% of Day 14 values.

Plasma gastrin concentrations and total gastrin AUC also increased in a dose- and time-related manner in response to RBP treatment, with the increases in gastrin AUC reaching statistical significance compared to placebo by Day 5 of treatment. While there was a trend toward larger gastrin AUCs with higher RBP doses, the differences noted between dosage groups were not significantly different. The increases produced during RBP treatment were substantially reversed within 24 hr after the last dose (Day 15).

PK/PD Correlation

Correlation plots were constructed for the following PK/PD relationships from data obtained on Day 14: gastrin $AUC_{0-\infty}$ vs RBP $AUC_{0-\infty}$, gastrin $AUC_{0-\infty}$ vs RBP Cmax, mean intragastric pH vs RBP $AUC_{0-\infty}$, mean intragastric pH vs RBP Cmax, % time pH>3 vs RBP $AUC_{0-\infty}$, and % time pH>3 vs RBP Cmax. There were no apparent relationships between any of the variables observed for any of the plots.

In conclusion, the PK data suggest that the disposition of RBP was rapid and dose-proportional (based on oral clearance data) over a 10 to 40 mg dosing range. Some accumulation of drug appeared to occur over time, however, the extent was not statistically significant. Statistically significant dose-related increases in intragastric pH and plasma gastrin were observed. The effects on intragastric pH were significant for all doses studied. At steady-state, the relative effectiveness of the four treatment regimens at raising intragastric pH was: Placebo<10 mg RBP/day<20 mg RBP/day≡40 mg RBP/day. There were no apparent PK/PD relationships for the parameters examined.

2. Protocol #J081-004 – A placebo-controlled, ascending, multiple oral dose study to evaluate the safety, tolerance, and pharmacokinetics of E3810 in healthy male volunteers.

This was a randomized, placebo-controlled, double-blind, ascending multiple oral dose study to evaluate the safety and PKs of daily doses of RBP (20 and 40 mg) for 7 days to 18 healthy, male, Japanese volunteers (nine volunteers per treatment group: 6 active, 3 placebo).

Pharmacokinetics

Plasma concentrations of RBP were all below the assay LOQ (5 ng/ml) prior to each daily dose, indicating lack of accumulation with multiple dosing at both 20 and 40 mg. This conclusion was also confirmed by an examination of the Cmax and AUC values for each treatment after the first and last doses. The tmax after the last dose of 40 mg RBP was statistically significantly shorter than that observed after the first dose. The sponsor suggested that this could have been caused by the neutralization of gastric juice after initial RBP doses (due to the pharmacologic effect of the drug), with partial dissolution of the enteric tablet in the stomach as it is designed to release at higher pHs. Mean values for half-life, tmax, and Cl/F were not significantly different between the 20 and 40 mg doses. Mean values for Cmax and AUC did not increase proportionally with dose, with the values after the 40 mg dose less than predicted based on values observed after the 20 mg dose. The results of the PK calculations for RBP are provided in Table VII.13.

Table VII.13. Mean±SD PK parameters for RBP (N=6 for each group).

	20 mg		40 mg	
	First[1]	Last[2]	First	Last
$AUC_{0-\infty}$ (ng*hr/ml)[3]	863±492	897±336	1,296±552	1,036±308
Cmax (ng/ml)	478±124	407±136	595±199*	418±177
tmax (hr)	4.6±1.1	4.0±1.4	5.1±0.6**	3.8±0.7
Half-life (hr)[4]	1.03±0.56	1.34±0.70	0.90±0.19	1.49±0.78
Cl/F (ml/min/kg)	7.49±3.39	6.49±1.95	8.91±4.00	10.08±2.53

[1,2]Results are provided for RBP, S, and TE after the first and last doses (Days 1 and 7, respectively).
[3]AUCs were calculated as $AUC_{0-\infty}$ after the first dose and as AUC_{0-24hr} after the last dose.
[4]Calculated from the terminal 4 plasma concentration points
*$p<0.05$ for First vs Last, **$0.05<p<0.10$ for First vs Last

Although DM and DMTE could not be detected in the plasma of any subject during repeated qd dosing of 20 mg and 40 mg RBP, the TE and S metabolites were observed. There were very few plasma samples that contained detectable levels of S, whereas the TE metabolite appeared in greater quantities. Even though not statistically significant, there did appear to be some accumulation of TE by the last dose in both the 20 and 40 mg dosing regimens based on individual and mean Cmax and AUC values. The results of the PK calculations for both the S and TE metabolites are provided in the tables below.

Table VII.14. Mean±SD PK parameters for the S metabolite.

	20 mg		40 mg	
	First[1]	Last[2]	First	Last
$AUC_{0-\infty}$ (ng*hr/ml)	ND[3]	ND	ND	ND
Cmax (ng/ml)	27±14	13±14	24±19	10±16
Tmax (hr)	4.4±1.1 (n=5)[4]	3.0±1.0 (n=3)	5.1±1.3 (n=4)	4.3 (n=2)
Half-life (hr)	ND	ND	ND	ND
Cl/F (ml/min/kg)	ND	ND	ND	ND

[1,2]Results are provided for RBP, S, TE after the first and last doses (Days 1 and 7, respectively).
[3]ND - not determined
[4]Means are provided for 6 subjects unless indicated otherwise.

Table VII.15. Mean±SD PK parameters for TE (N=6 for each group).

	20 mg		40 mg	
	First[1]	Last[2]	First	Last
$AUC_{0-\infty}$ (ng*hr/ml)[3]	401±242	614±452	911±1,123	1,366±1,735
Cmax (ng/ml)	89±43	123±85	139±123	232±235
Tmax (hr)	5.3±0.8	4.8±0.8	5.4±0.5	5.3±0.6
Half-life (hr)[4]	2.66±0.65	2.29±0.27	2.53±0.68	2.44±1.02
Cl/F (ml/min/kg)	ND	ND	ND	ND

[1,2]Results are provided for RBP, S, and TE after the first and last doses (Days 1 and 7, respectively).
[3]AUCs were calculated as $AUC_{0-\infty}$ after the first dose and as AUC_{0-24hr} after the last dose.
[4]Calculated from the terminal 3 plasma concentration points.

Because no RBP, S, nor DM could be detected in the urine of the first 2 subjects in both studies, and because the sum of the cumulative amounts of TE and DMTE excreted into the urine were not more than 0.10% of the dose in either individual, these moieties were not quantified in the other subjects. TEC and its glucuronide conjugate were the primary metabolites found in urine, and their excretion was not dose-dependent.

Protein-binding

Serum protein-binding was measured using serum samples taken 5 and 7 hours after the last RBP dose during both the 20 and 40 mg dosing regimens. However, RPB concentrations in most of the samples were less than the detection limit (14-25 ng/ml) of the assay and only 5/48 samples could be quantified. Mean protein-binding was 96.3±1.0%, however, in view of the small sample size and lack of information regarding the analytical assay sensitivity, this value is of limited use.

Serum Gastrin

There were statistically significant increases in serum gastrin noted after both the 20 and 40 mg RBP doses when compared to predose values. Although it was difficult to draw a clear conclusion because of the large interday and intersubject variability in serum gastrin observed in both active and placebo groups, the data suggest that RBP resulted in elevation of fasting serum gastrin after repeated doses.

Table VII.16. Mean±SD fasting serum gastrin[1] concentrations (pg/ml).

	Placebo (N=3)	20 mg RBP (N=6)	Placebo (N=3)	40 mg RBP (N=6)
Predose	65±14	75.3±32.2	69.7±50.1	55±14.1
Day 5	50.3±2.9	88.8±32.5*	69.3±18.5	83±32.5
Day 8	91.7±14.8*	159.2±69.7*	95.3±23.5	111.3±24.4**
7 days post last dose	64.7±18	76.8±26.2	68±21.3	79.8±24.6

*p<0.05, **p<0.01(paired t-test vs predose for each group)
[1]Normal range (fasting): 37-172 pg/ml

In conclusion, RBP did not appear to accumulate after multiple daily doses of 20 mg or 40 mg and displayed less than proportional PKs. The S and TE metabolites were observed in plasma at both doses. Although the quantities of the S were too low to allow calculation of meaningful PK parameters, the TE metabolite revealed a trend to accumulate with multiple dosing. Only the TEC metabolite could be detected in urine in appreciable quantities; its excretion did not appear to be dose-dependent.

3. Protocol #J081-005 – A multiple oral dose study to evaluate the safety, pharmacokinetics, and pharmacodynamics of E3810 in healthy male volunteers.

Since the information contained in this study report was available from studies that were better designed and well-controlled, this study was not reviewed in depth.

E. Other Bioavailability Studies:

1. Protocol #A001-110 – An open-label, single-dose, absolute bioavailability study of 20 mg rabeprazole sodium administered intravenously and orally in healthy volunteers.

This was a randomized, balanced, open-label, two-period, two-treatment, two-way crossover study in 28 healthy male and female volunteers to determine the absolute BA of a 20 mg RBP tablet (to-be-marketed formulation) in comparison with a 20 mg intravenous RBP dose.

The PK parameters are provided in Table VII.17. Two subjects had no detectable levels of RBP following oral administration.

Table VII.17. Means±SD PK parameters for RBP.

PK Parameter	Treatment	
	20 mg oral (N=26)	20 mg iv (N=28)
Cmax (ng/ml)[a]	441±216	1646±461
Tmax (hr)[a]	4.2±1.2	0.1±0.1
$t_{½}$ (hr)[b]	1.5±0.8	1.0±0.6
$AUC_{0-\infty}$ (ng*hr/ml)[a]	709±319	1290±357
AUC_{0-24} (ng*hr/ml)[a]	689±318	1280±357

[a]p-value = 0.0001
[b]p-value = 0.0122

Statistically significant treatment differences were observed for all PK parameters. The absolute BA ($AUC_{0-\infty,po}/AUC_{0-\infty,iv}$) of RBP was shown to be 51.5% as per ANOVA of log-transformed data. Total body clearance following iv administration was 283±98 ml/min (sponsor's analysis) and approximately 243 ml/min following oral administration as calculated by

this reviewer ($Dose_{po}$*F/$AUC_{0-\infty, po}$). Although there was a statistically significant difference in the half-life values for oral and iv administration, the intersubject variability was relatively high.

2. Protocol #J081-027 - **A single-dose study to evaluate the absorption of E3810 after administration as an enteric-coated tablet or in a sodium bicarbonate solution in healthy male volunteers**

This was a randomized, open-label, crossover study in 10 healthy, male, Japanese subjects to evaluate the absorption of RBP after administration as an enteric-coated tablet or as a sodium bicarbonate solution (intended to mimic conditions of increased stomach pH).

RBP was rapidly absorbed when administered in sodium bicarbonate solution, even when it was directly released into the stomach. Tmax values ranged from 7.5 to 30 minutes. In addition, statistically significantly higher AUC_{0-12} and Cmax values were obtained with RBP in sodium bicarbonate solution than when administered as an enteric-coated tablet. These results were attributed to the differences in the degradation and elution processes of the formulations. There were no significant differences in half-life values between the two treatments. The PK results are displayed below.

Table VII.18. Mean±SD PK parameters for RBP.

	Cmax (ng/ml) (N=10)	Tmax (hr) (N=10)	AUC_{0-12hr} (ng*hr/ml) (N=10)	Half-life (hr) (N=10)
RBP Tablet	422.9±214.8	4.8±2.0	850.2±348.2[a]	1.5±1.1[a]
RBP Solution	1621.7±1023.2[b]	0.3±0.2[b]	1319.1±617.5[b]	1.1±0.5

[a]N=9 as one subject in the tablet group had no elimination phase.
[b]Significantly different ($p<0.01$) from tablet.

Reviewer's Comment: The sponsor does not intend to market a RBP solution.

3. Protocol #J081-003 - **A single oral dose crossover study to evaluate the effect of food on the pharmacokinetics of E3810 in healthy male volunteers.**
This was a randomized, two-way crossover study in 12 healthy, male, Japanese volunteers to evaluate the effect of food on the PKs of RBP after a single oral dose. Each volunteer received a single, 20 mg oral dose of RBP (as 2x10 mg tablets) after fasting and after a standard breakfast.

Table VII.19. provides the PK results for RBP from both the fasting and fed groups. There were statistically significant differences observed for tmax and half-life, however, it should be noted that blood was sampled for only 12 hours after the RBP dose. Approximately half of the subjects in both groups had significant plasma concentrations of RBP at 12 hours, therefore, the terminal elimination phase may not have been adequately characterized. In addition, since neither AUC_{0-12} nor AUC_{0-24} were reported, it is difficult to assess the validity of the $AUC_{0-\infty}$ values.

Table VII.19. Mean±SD PK parameters for the food effect study.

	Fasting (N=12)	Non-fasting (N=12)
$AUC_{0-\infty}$ (ng*hr/ml)	937±617	901±544
Cmax (ng/ml)	437±237	453±138
Tmax (hr)[a]	3.58±0.85	5.25±1.36
Half-life (hr)[a]	1.49±0.68	1.07±0.47
Cl/F (ml/min/kg)	8.75±6.11	8.53±5.18

[a]Statistically significant at $p<0.01$ as per ANOVA.

Reviewer's Comment:
The rate of RBP absorption was affected by a meal, as evidenced by a Tmax that was 1.7 hours longer after the meal compared with Tmax values under fasting conditions. However, the $AUC_{0-\infty}$ parameters could not be adequately assessed for the reasons listed above. Furthermore, there were other factors related to this study which probably resulted in suboptimal data/results, such as failure to perform the analysis of the PK parameters for BE using the Two One-sided Tests Procedure on log-transformed data, failure to administer the to-be-marketed 20 mg tablet strength of RBP, and failure to provide a meal which is consistent with the draft "Guidance for Industry: Food-Effect Bioavailability and Bioequivalence Studies." It is not known how RBP was administered with respect to food in the clinical trials, although it was given under fasting conditions in almost all of the PK studies. In conclusion, the validity of the results obtained in the current study cannot be substantiated. It is recommended that the sponsor perform another Food Effect Study which is consistent with the guidelines set forth in the draft "Guidance for Industry: Food-Effect Bioavailability and Bioequivalence Studies."

Conclusions from the PK and BA Studies
RBP exhibited approximately linear PKs at doses from 10 to 40 mg, and did not appear to accumulate with multiple dosing. Maximum plasma levels (Cmax) were observed from 1 to 5 hours after dosing (Tmax). The absolute BA of oral RBP was about 52%. The extent of BA for RBP when administered with food could not be adequately assessed.

RBP is metabolized primarily in the liver by the CYP450 enzyme system. Elimination was generally rapid, with plasma concentrations decreasing to <LOQ of the analytical assay in most studies by 16-24 hours after the last dose. The major metabolite detected in plasma after clinically relevant doses was the TE. No unchanged RBP was excreted into the urine, but the majority of the metabolites (90%) were cleared by the kidneys. The major metabolites detected in urine were the TEC and MA, and their respective glucuronides. Approximately 10% of the metabolites were eliminated via the feces.

F. Studies in Special Populations

1. Protocol #A001-003 - A pilot study of the safety, tolerance, and pharmacokinetics of E3810 in healthy male volunteers and in men with renal failure.

This was an open-label, single-center study in 20 males subjects to assess the safety, tolerance, and PKs of RBP in healthy male volunteers and in men with stable, end-stage renal failure, following a single oral administration of 20 mg RBP. Renal failure patients were studied for two inpatient periods, one on the day immediately following a hemodialysis treatment, and one during a hemodialysis treatment, with a two week washout period between drug administrations.

For the renal failure subjects, there were no statistically significant differences ($p>0.22$) in the PK parameters measured during hemodialysis compared to those measured the day after hemodialysis. Due to some outliers, some of the mean data were shifted to the right, however, non-parametric analysis confirmed that there were no significant treatment differences.

A subjective comparison of the PK parameters for the healthy subjects to those for the renal failure subjects did not reveal any **clinically** significant differences. However, there were inadequate plasma concentration data to calculate half-life values for some of the renal patients. This reviewer recalculated the half-life parameter for the evaluable subjects, and obtained values of 1.1 ± 1.0 hours for the renal patients during hemodialysis (N=7) and 0.9 ± 0.6 hours for these patients after dialysis (N=8), which are consistent with values obtained in healthy subjects. No