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 4. 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-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

Safety:
Abnormal symptoms, which were considered to be possibly related to the study drug, were reported in 3 subjects; these were rated as mild to moderate in severity and included upset stomach, diarrhea, and headache. No clinically significant changes were observed in ECG recordings, vital signs, or clinical laboratory tests. Several abnormal clinical laboratory results were observed, but none were considered likely to be related to RBP, although a relationship could not be excluded.

CONCLUSIONS:

RBP was generally well tolerated by all subjects. 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 UM-2 and UM-2 glucuronide could be detected in urine in appreciable quantities; their excretion was not dose-dependent.

REVIEWER'S COMMENTS:

1. The to-be-marketed formulation or strength of RBP was not used in this study. Furthermore, there were no linking BE studies with any of the formulations used in any of the PK or clinical studies.
2. Analytical validation for RBP and its metabolites in both plasma and urine was inadequate and/or unacceptable. Furthermore, the sponsor admits that "final procedures" for assay validation criteria were not established at the time this study was performed, therefore, no in-study validation data are available.
3. The protein-binding data are of limited value due to the small number of samples analyzed and the lack of data regarding the sensitivity of the analytical assay.
4. RBP was given with food in this study.
5. Overall, the validity of the results obtained in the current study are tentative due to the uncertainty regarding the BA of the formulation used and the inability of the analytical assay to reliably and accurately quantitate RBP and its metabolites in plasma and urine.

TITLE: 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

Protocol Number: E3810-J081-027

Study Dates: April 1995

OBJECTIVE: to evaluate the absorption of RBP after administration as an enteric-coated tablet or in a sodium bicarbonate solution (intended to mimic conditions of increased stomach pH)

METHODS:
Study Design: randomized, open-label, crossover study

Syudy Population: 10 healthy, male, Japanese subjects between the ages of 21 and 28 years

Treatment and Administration:
The 10 subjects were randomly divided into 2 groups of 5 subjects:
"Enteric-coated tablet" group - received one 20 mg tablet of RBP orally with 120 mL of water at 9:00 AM under fasting conditions, followed by 50 mL of water taken 10, 20, and 30 minutes after drug administration.
"RBP-$NaHCO_3$ solution" group - received 20 mg of RBP dissolved in 90 mL of 160 mM sodium bicarbonate solution administered at 9:00 AM under fasting conditions. This was immediately followed by 30 mL of sodium bicarbonate solution; another 50 mL of sodium bicarbonate solution was administered at 10, 20, and 30 minutes after RBP administration.

After a one-week wash-out period, subjects were received the alternate treatment. Lunch, supper, and a snack were served at 13:00, 18:00, and 21:00, respectively, on the study day.

Study Drug Supplies:
20 mg enteric-coated RBP tablet; #K39001ZZE. ***This is the to-be-marketed formulation.***
Sodium bicarbonate manufacturing number: 195011
Purified water manufacturing number: 195401

Pharmacokinetic Sampling:
The pharmacokinetic profile during the treatment phase was evaluated by measuring the concentrations of RBP in plasma. Blood was collected prior to and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, and 12 hours after RBP administration for the "enteric-coated tablet" group, and prior to and at 2.5, 5, 7.5, 15, 30, and 45 minutes, and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, and 12 hours after RBP administration for the "RBP-$NaHCO_3$ solution" group.

Pharmacodynamic Sampling:
Gastric pH monitoring and recording was conducted using a _____ from the time of administration of 120 ml sodium bicarbonate solution until about 1 hour after administration of the last 50 ml of sodium bicarbonate solution in the "RBP-$NaHCO_3$ solution" group.

Safety:
Assessed by physical examinations, vital signs, ECG, and clinical laboratory tests, including hematology, serum chemistry, and urinalysis.

Pharmacokinetic Methods:
Pharmacokinetic parameters were calculated using model-independent analysis. Cmax, $AUC_{0\text{-}12}$, tmax, and half-life were used to evaluate bioavailability.

Statistical Methods:
Statistical analysis of the difference in the mean pharmacokinetic parameters among the two formulations was conducted using ANOVA. The results of vital signs and clinical laboratory tests were analyzed using the paired *t*-test to compare the pre- and post-dose values.

Analytical Methods:
Plasma samples of RBP were quantified by [redacted], using an [redacted] method with [redacted] The following validation data were provided:
Linearity: r^2>0.999
Intraday Accuracy: 98-110% at 25 ng/ml and 96-106% at 1608 ng/ml
Intraday Precision: <8.5% CV
Interday Accuracy: 103% at 25 ng/ml and 102% at 1608 ng/ml
Interday Precision: ≤4% CV
Specificity: no major [redacted] in [redacted], however, no study sample [redacted] provided
Recovery/Stability: no data provided
Also no precision nor accuracy data provided for [redacted] curves.

RESULTS:
Demographics:
All subjects were Japanese males; their mean ages, heights, and weights were 24.5 years, 172.7 cm, and 65.6 kg, respectively. Subjects in the two treatment groups were similar with regards to baseline characteristics.

Pharmacokinetics:
When RBP was administered in sodium bicarbonate solution, the plasma concentration rapidly reached tmax in 7.5 to 30 minutes. In addition, statistically significantly higher $AUC_{0\text{-}12}$ 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.

Table 1. Mean±SD RBP pharmacokinetic parameters.

	Cmax (ng/ml) (N=10)	Tmax (hr) (N=10)	$AUC_{0\text{-}12hr}$ (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.

Pharmacodynamics:
Gastric pH rose to a value of 7-8 after drug administration in the "RBP-$NaHCO_3$ solution" group during the monitoring period.

Safety:
Adverse events were mild and resolved without treatment. Although some laboratory parameters revealed statistically significant changes from baseline, none were considered clinically significant. No significant abnormal findings in vital signs or 12-lead ECGs were observed throughout the study.

CONCLUSIONS:
RBP was rapidly absorbed even when it was directly released into the stomach. Bioavailability from a sodium bicarbonate solution was statistically significantly greater when compared to an enteric-coated tablet. In addition, both formulations of RBP were well tolerated at a dose of 20 mg.

TITLE: An Open-Label, Single-Dose, Absolute Bioavailability Study of 20 mg Rabeprazole Sodium Administered Intravenously and Orally in Healthy Volunteers

Protocol Number: E3810-A001-110

Study Dates: June-July, 1996

OBJECTIVES: to determine the bioavailability of 20 mg RBP tablets in comparison with intravenous administration of 20 mg RBP

METHODS:

Study Design: randomized, balanced, open-label, two-period, two-treatment, two-way crossover study

Study Population: 28 healthy male and female volunteers, between the ages of 18 and 45 years, and within 15% of normal body weight range

Treatment and Administration:

Study Period 1: 1 x 20 mg RBP tablet or a single 20-mg RBP 5-minute intravenous infusion
Study Period 2: subjects received the alternate treatment
All doses were given after a 10-hour fast followed by an additional 4 hours of fasting. There was a 7-day washout period between treatments.

Study Drug Supplies:

20 mg enteric-coated RBP tablets; #K5Y006ZZA. ***This is the to-be-marketed formulation.***
20 mg RBP intravenous infusion; #16052004.

Biological Sampling:

Blood samples for the determination of RBP plasma concentrations were collected at 0 (predose), 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, and 24 hours after the oral tablet dose of RBP, and at 0, 5 (end of 5-minute infusion), 10, 15, 20, 25, 30, and 45 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, and 24 hours after the start of the infusion

Pharmacokinetic Analysis:

The following PK parameters were determined: Cmax, tmax, kel, $t_{½}$, AUC_{0-24}, $AUC_{0-\infty}$, Cl_T, and F (mean $AUC_{0-\infty, tablets}/AUC_{0-\infty, iv}$).

Statistical Analysis:

Mean PK parameters were calculated by and tested for statistically significant differences by using ANOVA with the GLM procedure of SAS. Log transforms were performed on values of AUCs and Cmax.

Safety and Tolerability:

The occurrence of adverse events was recorded. In addition, vital signs, EEGs, and clinical laboratory tests were monitored. Summary statistics were provided as necessary.

Analytical Methods:

RBP was analyzed by a validated assay using
Both pre-study validation and validation during the analysis of the study samples was performed and the results are provided below.

Pre-study Validation

samples:

$R^2 \geq 0.999$ for range of 5.5 to 444 ng/ml

Sensitivity - LOQ = 5.5 ng/ml

Quality control samples:

	Interday Precision -	Interday Accuracy -
16 ng/ml	4.2% CV	106%
88 ng/ml	2.0% CV	100%
333 ng/ml	2.2% CV	103.6%
	Intraday Precision -	Intraday Accuracy -
16 ng/ml	5.8% CV	87.5%
88 ng/ml	1.9% CV	96.6%
333 ng/ml	1.5% CV	100.9%

Specificity:

The majority of RBP and IS were well-resolved.

Mean Recovery:

RBP = 86.2% at 5.5 ng/ml, 96.8% at 111 ng/ml, 101% at 444 ng/ml

IS = 95.5%

Stability:

	16 ng/ml	88 ng/ml	333 ng/ml
30 hr at room temp	108%	101%	100%
24 hr at room temp	103%	94.9%	95.8%
71 hr at 2-8°C	102%	100%	101%
24.5 hr before extraction	100%	98.4%	99%
Freeze/thaw x 6	105.7%	98.6%	99.4%
61 wk at –70°C	96.5%	85.4%	86.5%

Intra-Study Validation

samples:

Linearity - $r^2 \geq 0.999$ for range of 5.5 to 444 ng/ml

Sensitivity: LOQ=5.5 ng/ml

Interday Precision - ≤8% CV

Interday Accuracy - >92%

Quality control samples:

Interday Precision - <10% CV

Interday Accuracy - >96%

Specificity:

QC and SC for RBP and IS were well-resolved. A number of from study samples were included and found to be acceptable.

RESULTS:

Demographics:

The mean age, height, and weight of the subjects was 30.2 years, 173.5 cm, and 68.4 kg, respectively. Of the 28 subjects, 16 were female and 12 were male, while 21 were Caucasian and 7 were Hispanic.

Safety:
There were 23 AEs, 19 of which were reported during the iv administration of RBP. None of these were judged to be serious and no subject withdrew from the study. There were no clinically significant abnormal lab values, vital signs, nor ECG results recorded during the study.

Pharmacokinetics: PK parameters are provided in Table 1. Two subjects had no detectable levels of RBP following oral administration. Mean plasma concentration vs time profiles following both iv and oral dosing are attached as Figure 1.

Table 1. PK Parameters of RBP.

PK Parameter	Treatment (Means±SD)	
	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

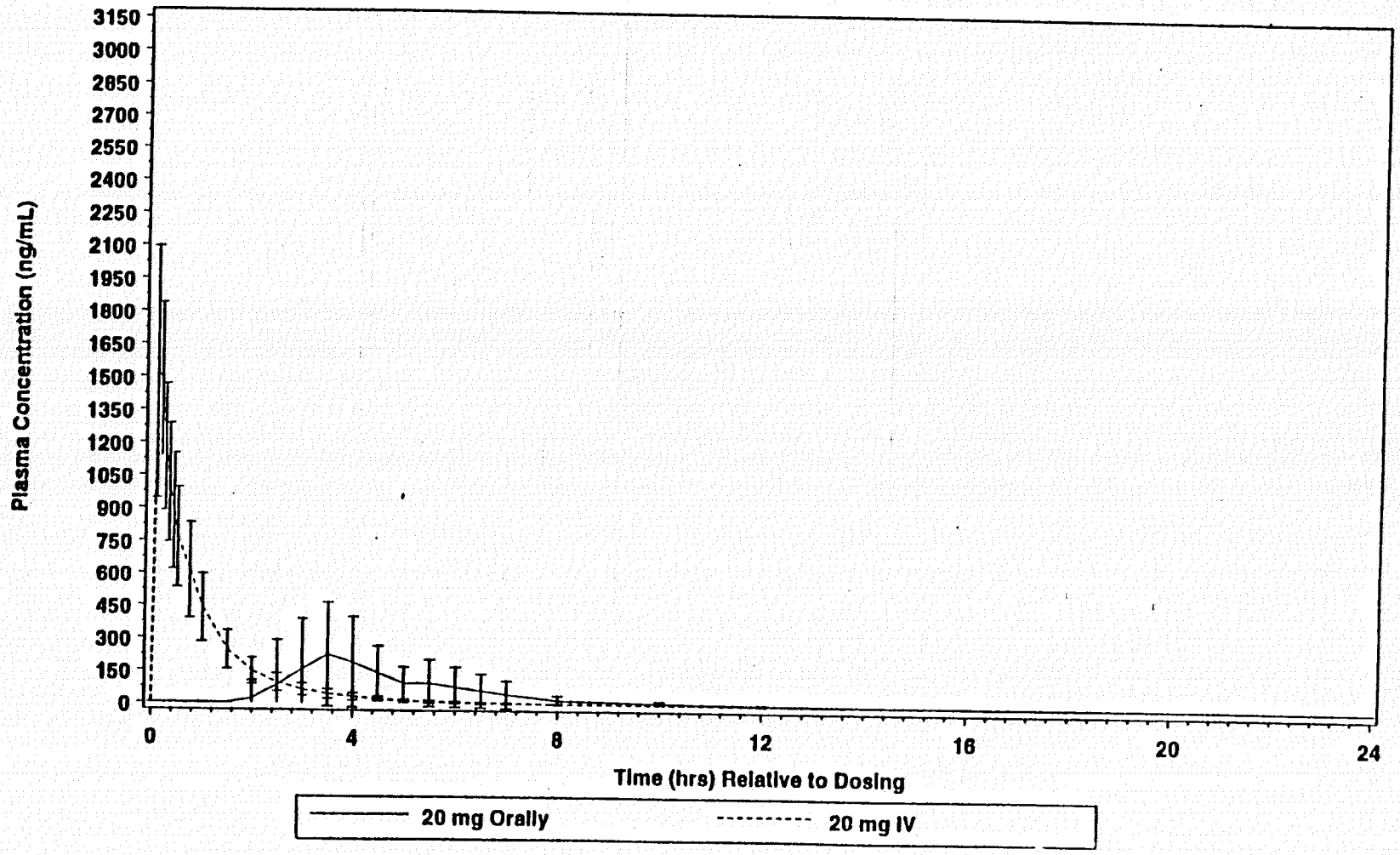
Statistically significant treatment differences were observed for all PK parameters. There were also significant sequence differences noted for the analysis of both AUC parameters and Cmax, which could confound the results. However, upon examination of the SAS data printout, this reviewer noted that sequence effect was tested using the residual error from the ANOVA as the error term, instead of using the mean-square error for subjects nested within sequence as the error term as stated in the study protocol. Therefore, the significance of this result is unknown.

The absolute BA of RBP was shown to be 51.5% as per ANOVA of log-transformed values of $AUC_{0-\infty}$. 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 high (range=0.45-3.19 hr and 0.52-4.06 hr for oral and iv dosing, respectively).

CONCLUSION:
Intravenous administration of RBP was associated with a higher incidence of AEs than the oral formulation, however, the AEs were self-limiting, predominantly mild in intensity, and resolved without treatment. As expected from intravenous administration, plasma concentrations of RBP were higher and peak concentration corresponded to the end of the short (5 minutes) infusion. The absolute BA of RBP after oral dosing was approximately 51.8%.

EISAI CORPORATION OF NA
E3810-A001-110
AN OPEN-LABEL, SINGLE-DOSE, ABSOLUTE BIOAVAILABILITY STUDY OF 20 MG RABEPRAZOLE SODIUM ADMINISTERED INTRAVENOUSLY AND ORALLY IN HEALTHY VOLUNTEERS

Figure 1: Mean (+/-SD) Plasma Concentration vs. Time (linear) For All Evaluable Subjects



Values noted by <5.5 and <11 were set to zero.

TITLE: A single oral dose crossover study to evaluate the effect of food on the pharmacokinetics of E3810 in healthy male volunteers

Protocol Number: E3810-J081-003

Study Dates: October-November, 1988

OBJECTIVE: To evaluate the effect of food on the pharmacokinetics of RBP after a single oral dose in healthy male volunteers

METHODS:
Study Design: randomized, two-way crossover

Study Population: 12 healthy, male, Japanese volunteers

Treatment and Drug Administration:
Fasting group - 6 subjects received 20 mg oral RBP with 120 ml water after an overnight fast, followed by an additional 5 hours of fasting
Fed group - 6 subjects received 20 mg oral RBP 30 minutes after a standard breakfast. The meal consisted of 526 kcal (~39% fat).
After a one-week washout period, subjects were crossed over to the opposite treatment.

Study Drug Supplies:
10 mg enteric-coated RBP tablets; #K891503. ***This was not the to-be-marketed formulation nor strength.***

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

Pharmacokinetic Analysis:
Non-compartmental PK parameters were calculated using standard methods. Values were reported for AUC_{0-24}, $AUC_{0-\infty}$, Cmax, tmax, half-life, and Cl/F.

Safety:
Assessed via adverse events, vital signs, clinical labs, and ECGs.

Statistical Methods:
Statistical analysis using ANOVA was performed for PK parameters. The 90% confidence interval for the difference of the two means using the Two One-sided Tests Procedure and symmetrical confidence intervals were estimated.

Analytical Methods:
Performed by Eisai Co., Ltd., using an [redacted]/Pre-study validation: May-Sept, 1988. Analysis of study samples: Nov-Dec, 1988.

Pre-study Validation:		
		Quality Control
Linearity	>0.999 at 5-400 ng/ml	-
Sensitivity	5 ng/ml	-
Interday Precision	<15% CV	ND pre-study 1% CV at 200 ng/ml in-study
Interday Accuracy	95-130% at 5 ng/ml 95-126% at 10-1000 ng/ml (calculated retrospectively)	ND pre-study 107-117% at 200 ng/ml in-study
Intraday Precision	<7% CV	ND pre-study <3% CV at 200 ng/ml in-study
Intraday Accuracy	42-122% at 5 ng/ml 78-113% at 10-400 ng/ml (data calculated retrospectively)	ND pre-study
Specificity: from individual subjects 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.		

RESULTS:

Demographics:

All subjects were Japanese males ranging in age from 20-26 years. Mean weights and heights were 61.7 kg and 170.5 cm, respectively.

Pharmacokinetics:

Table 1 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 AUC_{0-12} nor AUC_{0-24} were either not calculated or not reported, it is difficult to assess the validity of the $AUC_{0-\infty}$ values.

	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.

Safety:

Adverse events were mild to moderate in severity. No clinically significant changes were observed in ECG recordings, vital signs, nor clinical laboratory values.

CONCLUSIONS:

RBP was generally well tolerated by all subjects. The rate of RBP absorption was affected by a meal as evidenced by a tmax that was 1.7 hours longer after a meal compared with that in a fasting condition. However, Cmax and $AUC_{0-\infty}$ were similar between the two treatments, therefore, no effect of food on the extent of bioavailability was observed.

REVIEWER'S COMMENTS:

1. Analysis of PK parameters for BE using the Two One-sided Tests Procedure was not performed on log-transformed data.
2. The to-be-marketed formulation and strength of RBP was not used in this study. Furthermore, there were no linking BE studies with any of the formulations used in either the PK or clinical trials.
3. Pre-study analytical validation was inadequate and/or unacceptable. Furthermore, the sponsor admits that "final procedures" for assay validation criteria were not established at the time this study was performed, therefore, no in-study validation data are available.
4. The content of the breakfast used in this study was not consistent with the draft Guidance for Industry - Food-Effect Bioavailability and Bioequivalence Studies", which recommends the meal provide approximately 1000 kcal, 50% of which are derived from fat.
5. It appears that blood was not sampled for an adequate length of time to adequately assess the terminal elimination phase for RBP, therefore, values for $AUC_{0-\infty}$, half-life, and Cl/F may not be valid.
6. It is unknown how RBP was administered with respect to food in the clinical trials.
7. Overall, the validity of the results obtained in the current study cannot be substantiated based on the following:
   - the recommended meal was not provided,
   - the to-be-marketed strength was not studied,
   - plasma RBP was not reliably quantitated,
   - and uncertainty regarding the validity of AUC values.

STUDIES IN SPECIAL POPULATIONS

TITLE: A Pilot Study of the Safety, Tolerance, and Pharmacokinetics of E3810 in Healthy Male Volunteers and in Men With Renal Failure

Protocol Number: E3810-A001-003

Study Dates: August, 1993-June, 1994

OBJECTIVES:
To assess the safety, tolerance, and pharmacokinetics of RBP in healthy male volunteers and in men with renal failure.

METHODS:
Study Design: open-label, single-center

Study Populations:
A total of 20 males subjects were enrolled.

Healthy cohort: 10 healthy men. For this population, any subject with a history of renal disease (i.e., acute nephritis or pyelonephritis) was excluded. Additionally, any subjects who had baseline laboratory tests of renal function (i.e., 24-hour urine total protein, β_2-microglobulin excretion, or creatinine clearance) that revealed abnormalities were excluded. Subjects in this cohort were required to have a 24-hour urine creatinine clearance >90 ml/min/1.73 m^2.

Renal Cohort: 10 men with stable, end-stage, renal failure requiring maintenance hemodialysis. 24-hour urine creatinine clearance was <5 ml/min/1.73 m^2. In addition, renal failure subjects could receive only those medications mutually agreed upon as acceptable by the investigator and sponsor prior to the subject's enrollment into the study.

Treatment and Drug Administration:
Healthy cohort: received a single 20 mg dose of RBP
Renal cohort: received a single dose of 20 mg on each of two separate occasions (one on the day after a hemodialysis treatment and one during a hemodialysis treatment). There was a 2-week washout period between dose administrations.

Study drug was administered after a fast of at least 8 hours with 250 ml water.

Study Drug Supplies:
20 mg enteric-coated RBP tablets; #B01517, #CT02420
The lot numbers provided are for the placebo tablets, however, all 20 mg RBP tablets were manufactured using the to-be-marketed formulation.

Biological Sampling:
Blood samples for the determination of plasma RBP concentrations were collected predose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours after drug administration.

Pharmacokinetic Methods:
The following pharmacokinetic parameters were estimated from the RBP plasma concentration-time profiles for each subject: $AUC_{0\text{-}24}$, Cmax, Tmax, half-life, and Cl_T.

Safety:
Assessed via adverse events, clinical laboratory evaluations, vital signs, and physical examination.

Statistical methods:
Summary descriptive statistics were provided for all PK parameters. PK parameters were compared within renal patients (during hemodialysis versus post-hemodialysis drug administration) using ANOVA and Wilcoxon's test. Comparison of PK data between the two cohorts (healthy subjects versus renal patients) were made descriptively, with the assumption that the two cohorts were fairly balanced with respect to collected demographic and background data.

Analytical Methods:
RBP plasma concentrations were quantified from March-July, 1994, at [redacted] using an [redacted]. Assay validation data are provided below.

Pre-study Validation:		
	[redacted]	Quality Control (samples were 16, 88, and 333 ng/ml)
Linearity	>0.999 at 5.5-444 ng/ml	-
Sensitivity	LOQ=5.5 ng/ml	-
Interday Precision	<6% CV	<6% CV
Interday Accuracy	96-104% at 5.5-444 ng/ml	98-101%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided
Specificity: RBP [redacted] with no interference		
Recovery: 86% at 5.5 ng/ml to 99% at 55 ng/ml.		
Stability: examined at 16, 88, and 333 ng/ml. 83-86% residual at room temp for 30 hours, 88-94% residual at room temp for 22 hours, 100-102% at 2-8°C for 71 hours, 99-110% residual at –20°C for 18 weeks, 95-99% after 3 freeze/thaw cycles.		
In-study Validation:		
	[redacted]	Quality Control (samples were 16, 88, and 333 ng/ml)
Linearity	>0.999 at 5.5-444 ng/ml	-
Sensitivity	LOQ=5.5 ng/ml	-
Interday Precision	<7% CV	<8% CV
Interday Accuracy	99-111% at 5.5-444 ng/ml	100-103%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided
Specificity: Many of the study samples [redacted] submitted had poorly formed RBP [redacted] concentrations and unstable baselines.		

RESULTS:
Demographics:
Of the 20 subjects who completed the study, 15 were Caucasian, 3 were of African descent, and 2 were native Americans. The mean ages, heights, and weights for the subjects in the healthy cohort were 42.6 years, 174.8 cm, and 77.3 kg, respectively. Renally impaired subjects had mean ages, heights, and weights of 43.9 years, 172.7 cm, and 75.4 kg, respectively. All subjects in the healthy cohort had creatinine clearance values ≥90 ml/mim/1.73m^2, while all the renal failure subjects had values ≤5.4 ml/mim/1.73m^2.

Pharmacokinetics:

For the renal failure subjects, there were no statistically significant differences ($p>0.22$) in the PK parameters measured during hemodialysis and 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 kinetic parameters for the healthy subjects with those for the renal failure subjects did not reveal any clinically significant differences. However, there was inadequate plasma concentration data to calculate half-life values for some of the renal patients. Recalculation of the half-life parameter by this reviewer revealed values of 1.1±1.0 hours for the renal patients receiving dialysis (N=7) and 0.9±0.6 hours for these patients after dialysis (N=8), which are consistent with values obtained in healthy subjects. The following table provides the mean and median PK parameters for each treatment regimen.

	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.

Safety:

There were no deaths or withdrawals from the study, nor were there serious adverse events for the healthy subjects. Three renal failure subjects had serious adverse events that were considered unrelated to RBP, but all completed the study. One subject developed a *Pseudomonas* infection at the site of the hemodialysis shunt, and was treated with antibiotics. Another subject had clotting in the Perma-Cath that required hospitalization and Urokinase treatment. The third subject developed pain in the left hip that required hospitalization and treatment with antibiotics.

Mild or moderate adverse events were reported for 7/10 renal failure subjects and 1/10 healthy subject. Only single cases of abdominal gas and headache were considered possibly related to RBP. For renal failure subjects, the frequency of adverse events was somewhat higher during hemodialysis compared to post-hemodialysis.

Two subjects with renal failure and one healthy subject showed clinically significant changes in some hematology and clinical chemistry parameters, but these were not considered to be related to RBP administration. The changes for the renal failure subjects were considered to be probably related to the renal condition. There were no other clinically significant changes in clinical laboratory parameters. In addition, there were no clinically significant abnormalities in ECG recordings or vital signs.