TITLE: A cross-over study to evaluate the bioequivalency of 5 mg and 10 mg E3810 tablets in healthy male volunteers

Protocol Number: E3810-J081-010

Study Dates: April-July 1990

OBJECTIVE: To evaluate the BE of 2x5 mg and 1x10 mg RBP tablets in healthy male volunteers

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

Study Population: 24 healthy, Japanese, male volunteers

Treatment and Administration:
12 subjects received 2x5 mg of RBP and 12 subjects received 1x10 mg RBP with 120 ml water after an overnight fast. Subjects remained fasting until 5 hours after dosing. After a one-week washout period, subjects were crossed over to the opposite treatment.

Study Drug Supplies:
5 mg enteric-coated RBP tablets; #K032700. ***The sponsor does not intend to market a 5 mg tablet.***
10 mg enteric-coated RBP tablets; #K032100. ***This was not the to-be-marketed formulation or strength.***

Biological Sampling:
PK profiles were evaluated by measuring plasma concentrations of RBP. Blood was collected prior to dosing and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, and 24 hours after RBP administration.

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

Safety: Assessed by physical examination, adverse events, and clinical laboratory testing.

Statistical Analysis:
ANOVA was performed on untransformed and log-transformed values of $AUC_{0\text{-}24}$ and Cmax. The Two One-sided Tests Procedure and the calculation of the 90% confidence intervals were performed to evaluate BE. The comparison of tmax between the two treatments were evaluated via the Wilcoxon signed-ranks test for matched pairs.

Analytical Methods:
Pre-analytical validation was performed by Eisai Co., Ltd., Tokyo. Study samples were quantitated by [redacted] using [redacted] Assay validation data are provided in the tables below:

Pre-study Validation (5/88):		
Linearity	>0.999 at 5-400 ng/ml	Quality Control
LOQ	5 ng/ml	-
Interday Precision	<15% CV	-
Interday Accuracy	NR	ND
Intraday Precision	<10% CV	ND
Intraday Accuracy	NR	ND
		ND
Specificity: No blank curve, nor QC samples submitted.		
Recovery: Ranged from 112% at 5 ng/ml to 86% at 400 ng/ml with <7% CV.		
Stability: 100% residual at room temperature for 30 min, 101% residual at 20°C for 10 months, >95% at 98 ng/ml after 4 freeze/thaw cycles.		
In-Study Validation (8/90):		
Linearity	>0.995 from 30.7-122.7 ng/ml >0.995 from 122.7-981.5 ng/ml	Quality Control (200 ng/ml) -
LOQ	10 ng/ml	-
Interday Precision	NR	<3% CV
Interday Accuracy	NR	98%
Intraday Precision	NR	<5% CV
Intraday Accuracy	NR	>96%
Specificity: did not reveal potential interference. Also included were 1 QC (245 ng/ml), 1 LOQ, and 2 individual subject sample which were acceptable.		

RESULTS:

Demographics:

Three subjects intentionally did not swallow the tablets and were excluded from the study. Their data were replaced by those from an additional 3 subjects who participated in the same study method about 2 months after the scheduled study period. All subjects who completed the study were Japanese males. Their mean ages, heights, and weights were 23.4 years, 171.7 cm, and 64.1 kg, respectively. The two treatment groups were closely matched for these characteristics.

Pharmacokinetics:

Mean±SD PK parameters and the results of the BE analysis are provided in the table below.

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

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

Although $AUC_{0-\infty}$ was not determined in this study, no subject had any detectable plasma levels of RBP at 24 hours for either treatment. Furthermore, the majority of the last detectable plasma concentrations were near the assay LOQ for most of the subjects, therefore, values for AUC_{0-24} and $AUC_{0-\infty}$ were not likely to be significantly different. The data in this study indicates that 2x5

mg RBP tablets were equivalent to a 1x10 mg RBP tablet according to the Two One-Sided Tests Procedure and 90% confidence interval range of 80-125% using log-transformed data for AUC_{0-24}, but not for Cmax. The result of the Wilcoxon ranked sign test for tmax showed no statistically significant ($p>0.258$) difference between the two treatments.

Safety:
All reported symptoms were mild in nature and not drug-related. No clinically significant abnormal values in vital signs or clinical laboratory tests were observed during the course of the study. Abnormal findings in ECG readings were judged by the investigator not to be drug-related.

CONCLUSIONS:
RBP was generally well tolerated by all subjects as evidenced by the lack of drug-induced effects on vital signs, physical examination, electrocardiograms and clinical laboratory results.

The results for this study indicate that 2x5 mg RBP tablets were equivalent to a 1x10 mg RBP tablet according to the Two One-Sided Tests Procedure and 90% confidence interval range of 80-125% using log-transformed data for AUC_{0-24}, but not for Cmax.

REVIEWER'S COMMENTS:
1. Pre-study analytical validation was inadequate and/or unacceptable. Although the in-study validation provided some additional data, there were still inadequacies; i.e., QC samples examined at only one concentration, no precision/accuracy data for calibration curve concentrations, no chromatograms provided from individual subjects, change in the LOQ of the assay without
validation, etc.
2. Values for half-life and kel were not reported.
3. All subjects were not studied at the same time; data from 3 subjects was added on after completion of the initial study.
4. Neither the 5 mg nor 10 mg RBP tablets will be marketed. The 5 mg tablets were used in one clinical trial (not pivotal) and in one PD study (not reviewed).

TITLE: An Open-Label, Single-Dose, Bioequivalency Study of 2x10 mg Rabeprazole Sodium Tablets and 1x20 mg Rabeprazole Sodium Tablet in Healthy Volunteers

Protocol Number: E3810-A001-109

Study Dates: June-July 1996

OBJECTIVE: To evaluate the BE of RBP administered as 2x10 mg tablets versus a 1x20 mg tablet in normal, healthy, fasting volunteers.

METHODS:
Study Design: single-center, randomized, balanced, open-label, two-period, two-way crossover

Study Population: 24 normal, healthy, male or female volunteers between 18 and 45 years

Treatment and Drug Administration:
Study Period 1 - 1x20 mg RBP tablet to 13 subjects and 2x10 mg tablets to 12 subjects
Study Period 2 - subjects received the alternate treatment. 1x20 mg tablet to 11 subjects (one dropout from Period 1) and 2x10 mg tablets to 13 subjects.

There was a washout period of 7 days between Period 1 and Period 2. All doses were administered with 240 ml water after a 10-hour fast, followed by an additional 4 hours of fasting.

Study Drug Supplies:
20 mg enteric-coated RBP tablet; #K5Y006ZZA. ***This is the to-be-marketed formulation.***
10 mg enteric-coated tablets; #K55006ZZB. ***This was not the to-be-marketed formulation or strength.***

Biological Sampling:
Blood was collected prior to dosing and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, and 24 hours after drug administration for the determination of plasma RBP concentrations.

Pharmacokinetic Analysis:
AUC_{0-24}, $AUC_{0-\infty}$, Cmax, Tmax, kel, and half-life were determined using standard methods.

Safety:
Assessed by adverse events, clinical labs, physical examination, vital signs, and ECGs.

Statistical Analysis:
Mean PK parameters were tested for statistically significant differences by ANOVA using untransformed and log transformed data. Confidence intervals around the ratios resulting from the Two One-Sided Tests Procedure were calculated for all PK parameters. The two dosage forms were considered BE if the 90% confidence intervals for the ratios of the log transformed values of AUCs and Cmax were between 80 and 125%.

Analytical Methods:
Plasma samples were analyzed for RBP concentration at [redacted] in July, 1996 by an [redacted] method with [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	<7% CV	<9% CV
Interday Accuracy	96-108% at 5.5-444 ng/ml	99-100%
Intraday Precision	Not provided	<10% CV
Intraday Accuracy	Not provided	95-15%
Specificity: RBP [redacted] with no interference		
Recovery: 86% at 5.5 ng/ml to 101% at 444 ng/ml with <14% CV.		
Stability: examined at 16, 88, and 333 ng/ml. 100-108% residual at room temp for 30 hr, 96-103% residual at room temp for 24 hours, 100-102% after storage at 2-8°C for 71 hours, 87-97% residual after storage at -70°C for 61 weeks, 95-99% after 3 freeze/thaw cycles.		

In-study Validation:		
	[redacted]	Quality Control (samples were 33, 88, and 333 ng/ml)
Linearity	>0.999 at 5.5-444 ng/ml	-
Sensitivity	LOQ=5.5 ng/ml	-
Interday Precision	<7% CV	<12% CV
Interday Accuracy	98-103% at 5.5-444 ng/ml	100%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided
Specificity: RBP [redacted] with no interference in study		

RESULTS:

Demographics:

One subject withdrew from the study and did not receive the alternate dose of 1x20 mg RBP during Period 2. Of the 24 subjects who completed the study, 21 were Caucasian, 2 were Hispanic, and 1 was Asian. There were 12 males and 12 females. Subjects in the two treatment groups had very similar baseline characteristics; e.g., age, height, and weight.

Pharmacokinetics:

The concentration of RBP measured in the plasma of Subject 906 was <LOQ of the analytical assay for all but one sampling time during the 1x20 mg RBP treatment period, therefore, that subject's data was not included in the BE analysis. Summary statistics for each PK parameter (by treatment) for the remaining subjects are given in the table below.

Table 1. Mean±SD PK Parameters.

Ratios (%) and 90% Confidence Intervals* of the Ratio (RBP 2x10 mg/RBP 1x20 mg)			
PK Parameter	**Mean±SD RBP 2x10 mg (N=23)**	**Mean±SD RBP 1x20 mg (N=23)**	**Log-Transformed Data**
AUC_{0-24} (ng*hr/ml)	989.5±651.5	923.5±598.5	Ratio=107.5 (97.15;118.99)
$AUC_{0-\infty}$ (ng*hr/ml)	1004.6±657.5	941.3±605.0	Ratio=106.97 (96.99;117.98)
Cmax (ng/ml)	645.1±342.4	584.5±294.2	Ratio=110.90 (95.16;129.25)
Tmax (hr)	3.5±0.9	3.7±0.8	Not applicable
Kel (1/hr)	0.68±0.34	0.54±0.25	Not applicable
Half-life (hr)	1.4±1.0	1.6±1.0	Not applicable

*Confidence intervals are based on least square means.

In evaluating the PK parameters for Subject 907, it was noted that the Cmax for the 2x10 mg treatment was >3 SD from the mean for this treatment. Application of a mixture-model statistical outlier program confirmed that the Cmax for this individual was a statistical outlier. Table 2 provides the PK parameters excluding Subject 907.

Table 2. Mean±SD PK Parameters Excluding Subject 907.

Ratios (%) and 90% Confidence Intervals* of the Ratio (RBP 2x10 mg/RBP 1x20 mg)			
PK Parameter	**Mean±SD RBP 2x10 mg (N=22)**	**Mean±SD RBP 1x20 mg (N=22)**	**Log-Transformed Data**
AUC_{0-24} (ng*hr/ml)	885.5±443.9	877.8±569.9	Ratio=105.56 (95.35;116.86)
$AUC_{0-\infty}$ (ng*hr/ml)	899.3±446.8	893.2±572.4	Ratio=105.13 (95.28;116.00)
Cmax (ng/ml)	603.0±241.6	587.0±300.8	Ratio=105.43 (92.11;120.67)
Tmax (hr)	3.5±0.9	3.7±0.8	Not applicable
Kel (1/hr)	0.71±0.32	0.56±0.23	Not applicable
Half-life (hr)	1.2±0.6	1.4±0.5	Not applicable

*Confidence intervals are based on least square means.

The BE analysis was performed by this reviewer using the GLM procedure of SAS and the results obtained by the sponsor were confirmed. The results indicate that the two treatments were BE based on ANOVA and the Two One-Sided Tests Procedure using the 90% CI of the log-transformed data for AUC_{0-24}, $AUC_{0-\infty}$, and Cmax. There were no sequence or period effects observed for these parameters.

Safety:
There were no deaths or serious adverse events, nor were there any clinically significant out-of-range laboratory values or vital signs.

CONCLUSIONS:

RBP, administered as 2x10 mg tablets or 1x20 mg tablets, was equivalent based on the log-transformed data using the Two One-Sided Tests Procedure and the 90% confidence interval ranges for the AUC parameters, however, the BE criteria were not strictly met in all subjects for Cmax. If the Cmax value for one subject can be considered an outlier and excluded, then the BE criteria were met for Cmax as well. The sponsor's rationale is that the clinical efficacy of RBP is not dependent upon its peak plasma concentration, but rather the amount of drug absorbed and that, therefore, AUCs are the more relevant parameters to evaluate.

RBP was well tolerated by the subjects in this study whether administered as 2x10 mg tablets or a 1x20 mg tablet.

REVIEWER'S COMMENTS:

1. There were numerous blood sampling deviations (late draws) for several of the subjects.
2. The 10 mg tablets administered in this study were only administered in one of the pivotal clinical trials, #NRRK , for the maintenance of healing of GERD.

TITLE: An Open-Label, Single-Dose, Bioequivalency Study of Two Lots of 20 mg Rabeprazole Sodium Tablets in Healthy Volunteers

Protocol Number: E3810-A001-114

Study Dates: June-August 1996

OBJECTIVE: to compare the BE of RBP administered as a 20 mg tablet from two different manufacturing sites in normal, healthy, fasting volunteers.

METHODS:

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

Study Population: 28 healthy, male or female subjects between the ages of 18 and 45 years

Treatment and Drug Administration:

Study Period 1: 14 subjects each received one 20 mg RBP tablet manufactured at the site and 14 subjects each received one 20 mg RBP tablet manufactured at the site.
Study Period 2: Subjects were crossed over to the alternate treatment.

All doses were administered with 240 ml water 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: site - #K5X013ZZA, site - #K5Y006ZZA.
All tablets used in the clinical trials and PK studies were manufactured at the site.
The firm plans to manufacture future production-scale batches at the site. ***Both tablets are the to-be-marketed formulation.***

Biological Sampling:

Blood for the determination of plasma concentrations of RBP were obtained immediately prior to dosing (time 0), and at 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 post-dose.

Pharmacokinetic Analysis:

AUC_{0-T}, $AUC_{0-\infty}$, Cmax, Tmax, kel, and half-life were calculated using SAS.

Safety:

Assessed by adverse events, clinical laboratory abnormalities, and vital signs.

Statistical Methods:

Summary statistics were calculated for the PK parameters. The mean PK parameters were tested for statistically significant differences ($p<0.05$) due to sequence, subject (within sequence), period, and treatment by ANOVA using the GLM procedure of SAS for both untransformed and log transformed data (AUC_{0-T}, $AUC_{0-\infty}$, and Cmax). Ratios between the two lots of study drug were determined for all PK parameters. Confidence intervals (90%) around the ratios using the Two One-Sided Tests Procedure were calculated for AUC_{0-24}, $AUC_{0-\infty}$, and Cmax using the mean square error and least square means from the ANOVA.

Analytical Methods:

Study samples were analyzed for plasma RBP concentrations August-September, 1996, at [redacted] using [redacted] Assay validation criteria are provided below.

Pre-study Validation:		
	[redacted]	Quality Control (samples were 33, 88, and 333 ng/ml)
Linearity	>0.999 at 11-444 ng/ml	-
Sensitivity	LOQ=11 ng/ml	-
Interday Precision	<6% CV	<7% CV
Interday Accuracy	97-103% at 11-444 ng/ml	97-100%
Intraday Precision	Not provided	<6% CV
Intraday Accuracy	Not provided	88-101%
Specificity: RBP	with no interference	
Recovery: 86% at 5.5 ng/ml to 101% at 444 ng/ml with <14% CV.		
Stability: examined at 16, 88, and 333 ng/ml. 100-108% residual at room temp for 30 hr, 95-103% residual at room temp for 24 hours, 100-102% after storage at 2-8°C for 71 hours, 85-97% residual after storage at -70°C for 61 weeks, 98-106% after 6 freeze/thaw cycles.		
In-study Validation:		
	[redacted]	Quality Control (samples were 33, 88, and 333 ng/ml)
Linearity	>0.999 at 11-444 ng/ml	-
Sensitivity	LOQ=11 ng/ml	-
Interday Precision	<5% CV	<7% CV
Interday Accuracy	98-103% at 11-444 ng/ml	98-101%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided
Specificity: RBP	with no interference in study	

Note: During inspection of the analytical site, the Division of Scientific Investigations (DSI) found that the plasma concentrations of RBP were overestimated by 1% due to slight differences in the preparation of plasma aliquots for extraction. A difference this small in magnitude would not be expected to have a significant impact on the final PK parameters or analysis of the data.

RESULTS:

Demographics:

Three subjects were discontinued from the study because they withdrew consent to participate. The mean age of the 25 subjects who completed the study was 30±9 years. Twelve subjects were female and 13 were male. The mean height was 175.1±8.5 cm and the mean weight was 72.6±11.8 kg. Of the 25 subjects, 17 were Caucasian, 2 were of African descent, , 2 were East/Southeast Asian, and 4 were Hispanic.

Pharmacokinetics:

The mean PK parameters from the data analysis are provided in Table 1 below. The 3 subjects who withdrew consent and one other subject (#1423), for whom half-life, kel, nor $AUC_{0-\infty}$ could not be estimated, were excluded from the data analysis. Therefore, the evaluation of the ratios and 90% confidence intervals was based on data from 24 subjects.

Table 1. Mean±SD PK parameters for all evaluable subjects.

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

*CI are based on least square means.

This reviewer also did the ANOVA using the GLM procedure of SAS for the log-transformed data of AUC_{0-T}, $AUC_{0-\infty}$, and Cmax, and concurs with the results obtained by the sponsor. The mean AUC_{0-T} and $AUC_{0-\infty}$ data were equivalent based on the Two One-Sided Tests Procedure and the 90% CI of 80-125% for the log-transformed data. However, the Cmax was not BE based on the same criteria, with the Misato product resulting in mean values which were approximately 5% lower (untransformed data).

No significant effects due to sequence or period were observed in 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 or period effects were evident.

To summarize, the absorption of RBP from the drug product appeared to be delayed compared to the drug product, and resulted in decreased Cmax and increased tmax, although the AUC values were equivalent. Both of the formulations are delayed-release, enteric-coated tablets, and it may be that differences in the thickness of the enteric-coating resulted in delayed absorption in a sufficient number of subjects so that the two drug products had different Cmax distributions.

Safety:
There were no deaths nor serious adverse events. Two adverse events were reported; one case of mild dizziness considered possibly related to drug, and one case of moderate hematuria that was considered remotely related to drug. The exit urinalysis for one patient revealed a trace amount of blood in the urine. Results of the repeat urinalysis at 10 days demonstrated 1+ blood in the urine. This was considered remotely related to study drug. There were no other clinically significant abnormal laboratory values. There were no clinically significant out-of-range vital sign measurements.

CONCLUSIONS:

A single 20 mg RBP tablet manufactured at the site was equivalent to a single 20 mg tablet manufactured at the site based on ANOVA and the Two One-Sided Tests Procedure using the 90% confidence intervals of 80-125% for log-transformed data for AUC_{0-T}

and AUC_{∞}, but not for Cmax. In addition, tmax values for the Misato drug product were significantly longer.

REVIEWER'S COMMENTS:

1. No outlier test was performed on the subject who was dropped from the data analysis.
2. A gender analysis was performed using the data from this study, however, the $AUC_{0-\infty}$ values were invalid. The sponsor will be requested to reanalyze the data using the $AUC_{0-\infty}$ values submitted December 11, 1998.

BIOAVAILABILITY AND PHARMACOKINETIC STUDIES

TITLE: Excretion balance and pharmacokinetics in steady state after single dose oral intake of ^{14}C-E3810 in healthy volunteers

Protocol Number: E3810-E044-111

Investigators and Sites: [redacted]

Study Dates: June-July, 1996

OBJECTIVES:
1. to examine the excretion balance of radiolabelled RBP in urine and feces after a single oral dose of ^{14}C-RBP, preceded by once daily doses of RBP for 7 days.
2. to examine the plasma and whole blood concentration vs time curves for radiolabelled RBP.
3. to examine the metabolic profile of RBP in plasma, urine, and feces.

METHODS:
Study Design: open-label, single-treatment, single-center, PK and mass balance study

Study Population: 6 healthy male volunteers, between the ages of 45 and 65 years, and within 15% of normal body weight range

Treatment and Administration:
RBP tablets were administered as a single, oral, 20 mg daily dose at 8:30 AM for 7 days. ^{14}C-radiolabelled RBP was given as a single, oral, 20 mg dose in solution on Day 8 after a 10-hour overnight fast. The dose was individually calculated based on the amount of ^{14}C-radioactivity in the medication. To reduce degradation of RBP (secondary to acid lability), 50 ml of sodium bicarbonate solution (8 mmol/50 ml) was administered 2 minutes before, and at 10, 20, and 30 minutes after drug administration on Day 8. Subjects were fed standardized meals throughout the duration of the study.

Study Drug Supplies:
20 mg enteric-coated RBP tablets; #K5Y006ZZB. ***This was the to-be-marketed formulation.***

Test compounds to be used for the preparation of the ^{14}C-labelled RBP dose were supplied by [redacted] (^{14}C-RBP) and Eisai Chemical Co., Ltd. (RBP) as bulk material. From these test compounds, a final solution containing 20 mg/50 ml ^{14}C-RBP (50 µCi) was prepared and dispensed in individual containers by [redacted]

Biological Sampling:
Plasma and Whole Blood - Blood samples for the determination of total ^{14}C-radioactivity, as well as RBP and its metabolites, were collected just before the administration of the radiolabelled dose of RBP on Day 8 and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours post-dose.

Urine - Urine fractions were collected over the following intervals: 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, and thereafter in 24-hour intervals until subjects were discharged from the study.
Feces - All stool was collected quantitatively during the entire study. In addition, blank samples of urine and feces were collected before the first dosing of study medication on Day 1 and before the dosing of the radiolabelled drug on Day 8.

Pharmacokinetic Analysis:

Excretion Balance - The following PK parameters were determined for total ^{14}C-radioactivity in plasma, urine, and feces: Cmax, tmax, C_{24h} (plasma concentration at 24 hours after administration of radiolabelled drug), C_{24h}/Cmax, kel, half-life, AUC_{0-24}, $AUC_{0-\infty}$, C_{wb}/C_{pl} (ratio of ^{14}C-radioactivity in whole blood vs plasma), A_{urine} (total ^{14}C-radioactivity excreted in urine), A_{feces} (total ^{14}C-radioactivity excreted in feces), and A_{total} (total excreted ^{14}C-radioactivity).

Metabolic Profiling -

The metabolic profile for RBP and its metabolites in plasma was described qualitatively. The recoveries of RBP and its metabolites in urine and feces were expressed as a percent of the total radioactivity recovered for each individual collection interval. In addition, the quantity of RBP and its metabolites excreted in urine was also expressed as a percent of the total administered dose of radioactivity.

Statistical Analysis:

Excretion Balance -

Mean data and descriptive statistics were provided for all PK results. Medians were used to calculate tmax.

Metabolic Profiling -

Descriptive statistics and mean recovery data for RBP and its metabolites were provided.

Safety and Tolerability:

Subjects were queried daily to determine the occurrence of adverse events. In addition, vital signs, EEGs, and clinical laboratory tests were monitored.

Analytical Methods:

I. Excretion Balance

A. *Preliminary Methods Validation*: the plasma, whole blood, urine, and feces samples were analyzed for ^{14}C-radioactivity using a sensitive and specific liquid scintillation counting method. The preliminary methods validation parameters for each assay are displayed in Table 1.

Table 1. Methods validation parameters for the measurement of ^{14}C-radioactivity.

	Counting Efficiency	LOQ[a] (dpm)	Concentration Range (dpm)		Precision (%CV)		Accuracy	
			Intraday	Interday	Intraday	Interday	Intraday	Interday
Whole Blood	85%	50	71-1989 (n=6)	70-2099 (n=6)	<10%	≤10%	>93%	>94%
Plasma	90%	32	31-4078 (n=8)	31-4078 (n=8)	<10%	<11%	>93%	>95%
Urine	93%	47	71-4973 (n=9)	71-5226 (n=9)	<6%	<5%	>93%	>97%
Feces	85%	60	98-10148 (n-9)	98-10148 (n-9)	<7%	<13%	>94%	>95%

[a]LOQs were set at twice the background radiation counts.

B. *Analytical Validation*: study samples were analyzed in the single mode plus 15% in duplicate for plasma, whole blood, and urine. All feces samples were analyzed in duplicate. Two blank matrix and 6 quality control samples were included in each analytical run in order to determine the precision and accuracy of the assay. The assay validation parameters for analytical runs containing study samples are listed below.

1. Quench Curves - adequate efficiency ranges with good shape for all matrices.