Statistical methods:
The pharmacodynamic variables were summarized using descriptive statistics.
Statistical analyses were conducted on the following endpoints:

- Percentage of time pH>3 and pH>4
- Total AUCs and partial AUCs of intragastric acidity over 24 hours on Day 1 and Day 8.
- Total AUC and partial AUCs of plasma gastrin concentration over 24 hours on Day 8.

The total AUC values were derived from the 24-hour data and the partial AUC values derived from four meal-related intervals as follows: morning (08:00-13:00 hours), afternoon (13:00-19:00 hours), evening (19:00-22:00 hours) and night (22:00-08:00 hours). Differences among treatments for the total and partial AUCs for these variables were assessed by an ANOVA model suitable for a three-period cross-over study. The model included the terms for group, subject nested within group, period, and study medication effects.

RESULTS:
Demographics:
23/24 enrolled subjects completed this clinical trial according to protocol specifications. One subject discontinued from the study after receiving seven of the eight doses of RBP in the first dosing period; he did not receive OMP or placebo, therefore, his data was not included in the statistical analysis. Subjects enrolled in the six dosing sequences were comparable in demographic and baseline characteristics. All were *H. pylori* negative, with a mean age, height, and weight of 22.7 years, 177.0 cm, and 74.9 kg, respectively. The majority were Caucasian (18/24), while 5/24 were Western Asian, and 1/24 was listed as "other".

Pharmacodynamics Results:
Percent of Time pH>3 or pH>4
The mean percent of time over the 24-hour monitoring period that pH>3 or pH>4 on Day 1 and Day 8 was statistically greater for RBP (range: 44-69%) than that for OMP (range: 25-59%) or placebo (range: 8-22%). These results are depicted in the following table. The maximum median intragastric pH on both Day 1 and Day 8 was observed at 8 hours following RBP administration; profound reductions in gastric acidity were observed at this time as well.

Table 1. Summary of Mean±SD % Time pH>3 and pH>4

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

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

Intragastric Acidity:
At all time intervals for AUC on Day 1 and Day 8, the intragastric acidity was statistically significantly lower for the RBP and OMP treatments compared to placebo, indicating a significant effect of the proton-pump inhibitors on intragastric acidity both after the first dose and at steady-state. On Day 8, mean total AUC showed a reduction of 79% in integrated intragastric acidity over the 24-hour period following RBP administration in comparison to the period during which the subjects received placebo. There were no statistically significant differences observed between RBP and OMP for any of the AUC intervals on Day 8.

Table 2. Mean±SD Intragastric Acidity Data for Days 1 and 8.

Mean±SD AUC for Intragastric Acidity on Day 1 (mmol*hr/L)

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

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

Mean±SD AUC for Intragastric Acidity on Day 8 (mmol*hr/L)

AUC Interval (hours)	20 mg RBP (N=23)	20 mg OMP (N=23)	Placebo (N=23)
08:00 - 13:00	11±13[a]	20±33[a]	120±48
13:00 - 19:00	9±24[a]	31±47[a]	159±65
19:00 - 22:00	0.4±1.6[a]	3±10[a]	18±23
22:00 - 08:00	156±121[a]	218±161[a]	565±202
08:00 - 08:00	177±147[a]	271±229[a]	826±278

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

Non-parametric statistical analysis was also performed on the intragastric acidity data using the Wilcoxon signed rank test; the results were found to be similar to those discussed above.

Plasma Gastrin:
At every time interval during the 24 hours after dosing on Day 8, the mean partial and total AUCs of plasma gastrin for RBP were significantly greater than those for OMP and placebo. The mean AUCs for OMP were also found to be significantly greater than placebo at all time intervals. Plasma gastrin AUC results are displayed in Table 3.

Table 3. Mean±SD Plasma Gastrin AUC Data (pmol*hr/L).

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

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

Safety: There was one premature discontinuation from the study for reasons unrelated to safety, at Day 7 during the first dosing period. There were no deaths or serious adverse events in the study. All reported adverse events were mild or moderate in severity. No clinically important findings were observed for clinical laboratory evaluations or for vital signs.

CONCLUSIONS: In conclusion, this study demonstrated the following results in young, healthy, *H. pylori*-negative male subjects who completed eight-day dosing regimens of 20 mg RBP, 20 mg OMP, and placebo:

- Mean percentage of time gastric pH>3 and gastric pH>4 over a 24-hour time period on Day 1 and Day 8 were statistically significantly greater for RBP treatment as compared to both OMP and placebo.
- Intragastric acidity was statistically significantly reduced, with total $AUC_{08\text{-}08}$ after eight days showing 79% and 69% reductions during administration of RBP and OMP, respectively, in comparison to values obtained during placebo administration.
- Mean intragastric acidity was statistically significantly lower for RBP than OMP during the $AUC_{13\text{-}19}$, $AUC_{22\text{-}08}$, and $AUC_{08\text{-}08}$ time intervals on Day 1 of treatment, however, no differences were observed on Day 8.
- Mean plasma gastrin concentration curves following RBP and OMP were higher than those following placebo. In addition, gastrin concentrations were significantly greater after RBP administration as compared to OMP.
- RBP was well tolerated when compared to OMP and placebo.

REVIEWER'S COMMENTS:

1. The manner of reporting the "% of time that gastric pH was greater than a given value" is very misleading when using an intermittent pH monitoring method. The reader is left with the impression that the values reflect the percent of **time** gastric pH is maintained above a specified pH, when the values are really an indication of the number of **recordings** that gastric pH is maintained above a specified value.
2. There was large interindividual variability in the gastric acidity data.
3. Nine individual subjects had lower values for gastric acidity for OMP than for RBP on either Days 1 or 8.

TITLE: Rabeprazole effects on esophageal and gastric pH after single and multiple oral doses in patients with gastroesophageal reflux disease (GERD).

Protocol Number: L001-A (H4M-LC-NRRA)

Study Dates: August, 1993 – March, 1994

OBJECTIVES:
Primary - to examine the effects of RBP on esophageal and gastric pH in patients with GERD.
Secondary - to examine plasma gastrin levels following RBP dosing and
- to examine the clinical safety of RBP in patients with GERD.

METHODS:
Study Design: single-center, double-blind, randomized, two-way crossover study

Study Population:
20 male or female patients with GERD. Patients had clinically diagnosed GERD within a year of the start of the study. Patients also had pH measurements of ≤4 in the lower esophagus at admission for ≥10% of a 24-hour esophageal monitoring period.

Treatment and Administration:
Subjects were randomly divided into 2 treatment groups as follows:
Group 1: 20 mg RBP qAM for 7 days.
Group 2: 40 mg RBP qAM for 7 days.

Subjects were crossed over to the alternate treatment after a 7-day washout period.
Drug was taken after an overnight fast with 250 ml of water. Standardized meals were provided on the Baseline Monitoring Day, Dosing Days 1 and 7, and Day 8 of each treatment period. Breakfast, lunch, and dinner were provided 1-1.5 hours, 5-6 hours, and 10-11 hours after RBP administration, respectively.

Concomitant Therapy:
Patients were allowed to use acetaminophen for pain relief, but not allowed to take corticosteroids, NSAIDs, H_2-receptor antagonists, sucralfate, omeprazole, prostaglandins, anticholinergics, nor bismuth subsalicylate. Patients were also not permitted to take an antacid for a period of 90 minutes prior to and during pH monitoring during each treatment period. Patients were permitted to take antacids after dinner.

Drug Supplies:
RBP 20-mg tablets: #K31001ZZA/K31001ZZB. ***This is the to-be-marketed formulation.***
Matching placebo tablets: #KR2Y022AAZ/KR2Y002ZZB

Pharmacodynamic Sampling/Analysis:
For the purpose of determining reflux time, each patient was fitted with an ambulatory pH monitor on the Baseline Monitoring Day and Dosing Days 1 and 7 of each treatment period. A fully calibrated, double electrode was passed through the naris to measure gastric and esophageal pH. One electrode was placed at the lower esophagus and the other in the stomach; passage of the electrodes through the lower esophagus and stomach was verified by manometry. The pH monitor was worn for approximately 24 hours on the Baseline Monitoring Day and Dosing Days 1 and 7, and for approximately 24 hours on Day 8 of each treatment period. On the mornings

after the Baseline Monitoring Day, Dosing Day 2, and Day 9 of each treatment period, the pH electrodes were removed and re-calibrated.

The results of the esophageal and gastric pH monitoring from the Baseline Monitoring Day were downloaded on a microcomputer and analyzed for pH over time; the resulting reflux time was recorded on the CRF. If the gastroesophageal reflux time was ≥10% of the 24-hour esophageal pH monitoring period, patients were randomized to one of the two RBP treatment sequences.

Blood samples were obtained to determine plasma gastrin levels at hour 0 on the Baseline Monitoring Day and prior to and at 2, 3, 4, 6 and 8 hours after dosing on Dosing Days 1 and 7, and Day 8 of each treatment period. Plasma gastrin levels were measured by

Pharmacokinetic Sampling:
Blood samples were obtained to determine the plasma concentrations of RBP at 0, 2, 3, 4, 6 and 8 hours after dosing on Dosing Days 1 and 7 of each treatment period. Plasma concentrations were measured using a validated

Safety: Assessed by adverse events, ECGs, vitals signs, and clinical laboratories.

Statistical Methods:
Pharmacodynamics -
The primary response variables were mean and median gastric pH and reflux time, defined as the time (in percent) of the 24-hour observation period over which the lower esophageal pH was ≤4. A dose was considered effective when the reflux time had been reduced to ≤5% of the 24-hour monitoring period. Secondary response variables were the number of reflux episodes (total and those >5 minutes).

For Baseline, Dosing Days 1 and 7, and Day 8 for each RBP dose, both the primary and secondary response variables were summarized with descriptive statistics. Differences in RBP doses for all PD parameters were assessed using an ANOVA model with effects for sequence, patients within sequence, period and RBP dose. Carry-over effects were examined in the ANOVA model, and the Period 1 and Period 2 baseline parameters were compared. Differences in single-dose and multiple-dose parameters were assessed within each RBP dose using an ANOVA model with effects for sequence, patients within sequence and day.

Differences in effectiveness rates, GERD diagnosis continuation rates, and in rates of reductions to no reflux episodes >5 minutes between the doses of RBP were assessed using McNemar's test, with the continuity correction.

Plasma Gastrin -
For plasma gastrin levels, the $AUC_{0\text{-}8}$, Cmax, and tmax were determined for Dosing Days 1 and 7 and Day 8 for each RBP dose, and were summarized using descriptive statistics. Differences between RBP doses with respect to $AUC_{0\text{-}8}$, Cmax, and tmax were assessed by ANOVA as described above.

Pharmacokinetics -
Cmax and tmax were summarized for Dosing Days 1 and 7 for each RBP dose with descriptive statistics. Differences between RBP doses with respect to Cmax and tmax were assessed using ANOVA as described above.

RESULTS:

Demographics:

All enrolled patients completed the study. The two RBP treatment groups were similar with respect to baseline demographic characteristics. Overall means for age, height, and weight were 41 years, 69.7 inches, and 205.6 pounds, respectively. There were 15 males and 5 females in the study, and 19/20 subjects were Caucasian, while 1 subject was of African descent.

Pharmacodynamics:

Reflux Time

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

Table 1. Summary of Mean±SD reflux time (%).

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

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

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

Table 2. Mean±SD reflux time (%) excluding subjects not meeting GERD criteria.

	20 mg RBP (N=15)	40 mg RBP (N=15)
Baseline	28.7±19.9	27.9±22.6
Day 1	16.2±19.9[a]	8.7±15.6[a]
Day 7	6.6±11.9[a,b]	2.6±5.3[a]
Day 8	21.3±18.1[c]	14.8±16.0[a,c]

[a]p<0.01 vs Baseline
[b]p=0.043 Day 7 vs Day 1 for 20 mg dose.
[b]p<0.01 Day 8 vs Day 7 for 20 and 40 mg dose.

Effective Reduction of Reflux Time

There were no statistically significant differences between the 20 mg dose and the 40 mg dose in reducing reflux time. On Day 1, effective reductions in reflux time (≤5%) were observed in 60% of patients taking the 40 mg RBP dose versus 45% taking the 20 mg dose (p=.453). Reflux time was reduced to ≤5% by both the 20 mg and 40 mg RBP doses in 7 patients, by only the 40 mg

dose in 5 patients, by the 20 mg dose but not the 40 mg dose in 2 patients, and by neither dose in 6 patients.

On Day 7, effective reductions in reflux time (≤5%) were observed in 90% of patients on the 40 mg RBP dose versus 75% on the 20 mg dose (p=.250). Reflux time was reduced to ≤5% by both doses in 15 patients and by neither dose in 2 patients. In the 3 remaining patients, only the 40 mg RBP dose reduced the reflux time to ≤5%; however, in 2 of these patients, the reflux time on the lower dose was only slightly above normal (5.9% and 5.4%).

On Day 8 (the day following the last dose of study drug), 35% of patients had effective reductions in reflux time on the 40 mg RBP dose versus 30% on the 20 mg dose (p=.999).

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

Reflux Episodes

The differences between doses in reducing the number of reflux episodes were not statistically significant. On Day 8, the day following the last dose for the treatment period, the number of reflux episodes remained reduced for both RBP doses but had returned to values slightly lower than Baseline values. Treatment-by-period interactions were not statistically significant and the direction of dose effects generally appeared consistent for Period 1 and Period 2. These results are summarized in Table 3.

Table 3. Mean±SD number of reflux episodes.

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

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

Reflux Episodes >5 Minutes

The differences between doses were not statistically significant. By Day 8 the number of reflux episodes >5 minutes remained reduced for both RBP doses but had returned to values similar to the first day of dosing. Treatment-by-period interactions were not statistically significant and the direction of dose effects generally appeared consistent for Period 1 and Period 2. Results are summarized in Table 4.

Table 4. Mean±SD number of reflux episodes >5 minutes.

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

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

Number of Patients With No Reflux Episodes >5 Minutes

At baseline, all 20 patients in the study experienced at least one reflux episode of more than 5 minutes duration. Two and 5 patients (10% and 25%) on 20 and 40 mg RBP, respectively, had no reflux episodes >5 minutes on the first day of dosing. Nine and 15 patients (45% and 75%) on 20 and 40 mg RBP, respectively, had no reflux episodes >5 minutes on the seventh day of dosing. This difference was statistically significant (p=0.041). On Day 8, the day following the last dose for the treatment period, 18 and 17 patients on 20 and 40 mg RBP, respectively, experienced reflux episodes >5 minutes.

Gastric pH

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

Table 5. Mean±SD gastric pH.

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

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

Plasma Gastrin Concentration

Increases in plasma gastrin concentrations were seen with both RBP doses on the first day of dosing. Further increases were seen on the seventh day of dosing. Mean basal plasma gastrin concentration increased from 52.9±32.3 pg/ml at baseline to 81.1±45.4 pg/ml on Day 7 with the 20 mg RBP dose, and from 47.7±19.8 pg/ml to 71.5±36.5 pg/ml with the 40 mg dose. On Day 8 the plasma gastrin levels remained elevated for both RBP doses but had returned to levels only slightly higher than the first day of dosing.

The difference between the 20 mg and 40 mg RBP doses for $AUC_{0\text{-}8}$ on Dosing Day 7 was statistically significant (p=0.022). The differences between RBP doses for gastrin Cmax values were not significant. Mean tmax ranged between 5.7 and 7.3 hours for the two doses on the study days, but no trend was discernible.

The plasma gastrin AUC_{0-8} values and the results of the statistical analyses are summarized in Table 6.

Table 6. Mean±SD plasma gastrin AUC_{0-8}.

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

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

Pharmacokinetics:
The plasma concentrations of RBP were not suitable for a PK analysis because the concentrations of RBP were below the limit of quantification, not available, or not determined for the majority of samples. There were numerous errors when processing samples for the HPLC assay, therefore, any PK results should be interpreted with caution. As a result, there were insufficient data to adequately describe the PK time course of RBP. However, Cmax and tmax were determined for at least 9 patients for both treatment periods.

Consistent with linear PK, the Cmax for the 40 mg RBP dose was approximately twice the Cmax for the 20 mg dose on Dosing Days 1 and 7. For both RBP doses, Cmax was somewhat greater on Dosing Day 7 than on Dosing Day 1, however, the differences were not statistically significant.

Tmax was consistent for the two RBP doses: approximately 4.6 and 2.8 hours on Dosing Days 1 and 7, respectively. For both RBP doses tmax was earlier on Dosing Day 7 than on Dosing Day 1. The difference between dosing days approached statistical significance for the 20 mg dose and did reach statistical significance for the 40 mg dose.

Safety:
RBP, at doses of 20 mg and 40 mg, was generally well tolerated as assessed by adverse events, laboratory evaluations, vital signs, body weight, and ECGs. No clinically meaningful differences were observed between the two RBP doses with respect to these safety variables. No deaths or serious adverse events were observed during this study.

CONCLUSIONS:
This study revealed that both 20 mg and 40 mg doses of RBP administered for seven days to patients with GERD:

- Statistically significantly reduced reflux time.
- Statistically significantly reduced the number of reflux episodes (total and those >5 minutes).
- Statistically significantly increased intragastric pH.
- Statistically significantly elevated plasma gastrin levels.
- Were generally well-tolerated.
- There was no substantial advantage of 40 mg RBP over the 20 mg dose with regards to pharmacodynamic endpoints.
- There was a possible disadvantage of 40 mg RBP compared to 20 mg RBP with respect to elevations in plasma gastrin concentration.

REVIEWER COMMENTS:

1. This was only a crossover study design with respect to the individual subjects. Subjects did not receive RBP as a group during one treatment period and then cross over to the alternate treatment, rather, they were administered RBP at different times and dates.
2. Nearly 90% of the patients took antacids during the study, however, none were taken during the pH monitoring intervals.

APPENDIX I

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Table 6. Comparison between single-dose rabeprazole pharmacokinetic parameters in healthy, male, Japanese and American Subjects.

Dose = 10 mg			
Parameter or Variable (Mean ± SD)	Japanese Subjects (N = 30)	American Subjects (N = 16)	P-value Unpaired t-test
Wt (kg)	63.3 ± 9.32	76.6 ± 7.81	≤ 0.001
AUC (0 - ∞) (ng/mL)-h	505 ± 219	315 ± 204	0.006
CL/F (L/h)	23.4 ± 9.49	44.1 ± 21.1	0.002
CL/F/Wt (L/h/kg)	0.375 ± 0.156	0.572 ± 0.269	0.014
Dose = 20 mg			
Parameter or Variable (Mean ± SD)	Japanese Subjects (N = 74)	American Subjects (N = 39)	P-value Unpaired t-test
Wt (kg)	62.7 ± 6.17	76.7 ± 9.22	≤ 0.001
AUC (0 - ∞) (ng/mL)-h	969 ± 605	634 ± 302	≤ 0.001
CL/F (L/h)	29.9 ± 20.4	38.9 ± 18.1	0.022
CL/F/Wt (L/h/kg)	0.483 ± 0.335	0.516 ± 0.262	0.594
Dose = 40 mg			
Parameter or Variable (Mean ± SD)	Japanese Subjects (N = 10)	American Subjects (N = 14)	P-value Unpaired t-test
Wt (kg)	65.5 ± 8.54	78.5 ± 7.72	≤ 0.001
AUC (0 - ∞) (ng/mL)-h	1639 ± 705	1471 ± 810	0.603
CL/F (L/h)	29.9 ± 15.3	35.7 ± 19.5	0.442
CL/F/Wt (L/h/kg)	0.458 ± 0.225	0.461 ± 0.261	0.977

Table 7. Summary of PD Studies included in NDA 20-973

Study	Dosing Regimen	Study Population	PD Endpoint	Position of pH electrode	Duration of pH monitoring	Results
J081-007	10 mg x4 days 20 mg x4 days	Healthy Japanese	pH 4 holding time	Middle region of the stomach	Continuous for 24 hours	10 mg not different from baseline, Day 4 20 mg>baseline over 24 hours, Day 4
J081-008	20 mg in AM 20 mg in PM	Japanese, DU	pH 3 holding time	Greater curvature of stomach body	Continuous for 24 hours	AM dose>baseline for 24 hours, Day 4. PM dose>baseline for 24 hours, Day 4.
J081-018	20 mg x7 days	Healthy Japanese	Gastric acid: basal & gastrin-stimulated	Stomach	Continuous for 24 hours	No change in basal acid secretion vs baseline on Days 1 and 7. 90-100% decrease vs baseline after gastrin stimulation on Days 1 and 7.
J081-019	20 mg RBPx7 days 20 mg OMPx7 days	Healthy Japanese	pH 3 holding time Serum gastrin	Body of the stomach	Continuous for 24 hours	Increase in 24-hour pH 3 holding times on Day 7, but no differences between RBP and OMP. Increases in serum gastrin but no differences between RBP and OMP.
E044-106	20 mg RBPx14days Placebo x14 days	Healthy Caucasian	Endocrine function. Gastric acidity.	10 cm below GE junction in fundus of stomach	Four times hourly over 24 hours.	No changes in endocrine function tests, Day 14. Decreased gastric acidity on Days 7 and 14 for 24-hour period and four meal-related intervals compared to placebo.
E044-107	10mg, 20mg, 40mg, placebo x7 days	Healthy Caucasian	Gastric acidity Serum gastrin	Stomach	Hourly over 24 hours.	Decreased gastric acidity for all RBP doses over 24 hours on Day 7 vs placebo, but no differences between doses. All doses increased gastrin, but 40 mg>10mg and 20 mg.
E044-115	20 mg RBPx8 days 20 mg OMPx8 days	Healthy Caucasian	Time gastric pH>3,>4 Gastric acidity Plasma gastrin	Stomach	Hourly over 24 hours.	Increase in time pH>3, pH>4 for RBP and OMP vs placebo over 24 hours on Days 1 and 8, with RBP>OMP. Gastric acidity lower for RBP and OMP vs placebo over 24 hr on Days 1 and 8, but no difference between OMP and RBP. Gastrin greater with RBP and OMP vs placebo on Day 8, with RBP>OMP.
L001-A	20 mg x7 days 40 mg x7 days	Patients with GERD	Esophageal reflux time and episodes Gastric pH Plasma gastrin	Lower esophagus and stomach.	Continuous over 24 hours.	Decreased reflux time and episodes vs baseline on Days 1 and 7 for both doses, but no differences between doses. Higher gastric pH for both doses vs baseline on Days 1 and 7, with 40 mg>20 mg. Both doses increased gastrin on Days 1 and 7, with 40 mg>20 mg.

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Fig. 5

Rabeprazole Human (and Animal) Drug Metabolism Pathways