Statistical Methods:
Values for gastric juice, acid, and pepsin secretions obtained on Days 1, 7, and 8 were compared with those of Day 0 using a paired t-test (5% significance level).

RESULTS:
Pharmacodynamics:
<u>Basal secretion</u>: The amount of gastric juice secreted was reduced significantly when Day 0 levels were compared to Days 1 and 7 ($p \leq 0.05$). The amounts of acid secreted on Days 1, 7 and 8 were all lower than that on Day 0, however, these values were not statistically significant. Pepsin secretion was significantly lower on Days 1, 7 and 8 compared to Day 0 ($p \leq 0.05$).

<u>Gastrin-stimulated secretion</u>: Statistically significant decreases in the secretions of gastric juice ($p \leq 0.001$), gastric acid ($p \leq 0.001$), and pepsin ($p \leq 0.05$) were observed for Days 1, 7 and 8 compared to Day 0, with the suppression of acid secretion being particularly marked. The results for Day 8 suggested a partial recovery of gastric secretion.

The following table provides the percent decreases in gastric juice, acid, and pepsin secretions for all treatment and pH monitoring periods.

Table 1. Decreases (%) in gastric juice, acid, and pepsin secretions (means±SD).

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

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

Gastric juice pH exhibited marked increases on Days 1 and 7 during both basal and stimulated secretion, while on Day 8 a decline was observed, also indicating a partial recovery of gastric acid secretion.

Pharmacokinetics: No results reported (no reason provided).

Safety: No adverse drug reactions or other abnormal findings were observed.

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

statistical significance. These findings also suggest that gastric acid secretion begins to recover by 24 hours after a RBP dose.

REVIEWER'S COMMENTS:
1. There were a small number of subjects included in this study.
2. No information was provided regarding subject demographics, clinical laboratory values, or adverse events.
3. No individual nor raw data (including pH readings) were provided in this study report.
4. No PK analysis was performed as stated in the study protocol.

APPEARS THIS WAY
ON ORIGINAL

TITLE: A Comparison of the Effects of 7 Days Dosing of the Proton Pump Inhibitors E3810 (Rabeprazole Sodium) or omeprazole on Intragastric pH, and Serum and Urinary Gastrin Levels in Healthy Volunteers

Protocol Number: E3810-J081-019

Study Dates: March–August 1993

OBJECTIVE:
To compare the effects of RBP with those of OMP on gastric acid secretion in healthy volunteers.

METHODS:
Study Design: randomized, open-label, cross-over comparison between RBP and OMP

Study Population: 8 healthy Japanese volunteers without gastric mucosal atrophy. There were no restrictions on gender or ulcer history.

Treatment and Administration:
Subjects received daily oral doses of either 20 mg RBP or 20 mg OMP for 7 consecutive days. Drug was administered after breakfast. Subjects were crossed over to the alternate treatment after a washout period of at least ten days.

Gastric pH was measured during three 24-hour periods as follows:
Prior to drug administration; from 08:00 on Day 0 to 08:00 on Day 1
During drug administration; from 12:00 on Day 6 to 12:00 on Day 7
After completion of drug administration; from 08:00 on Day 8 to 08:00 on Day 9

Meals were provided to subjects at 08:00, 12:00, and 18:00 during the study. Smoking, alcohol consumption, and between-meal snacks were prohibited.

Drug Supplies:
20 mg enteric-coated RBP tablets; #K19007ZZD. *This is the to-be-marketed formulation.*
20 mg enteric-coated OMP tablets.

Pharmacodynamic Sampling/Analysis:
A micro pH glass electrode was inserted intranasally and the tip positioned in the body of the stomach. The sensor was connected to a portable pH recorder and intragastric pH was continuously recorded over the 24-hour time intervals listed above.

Biological Sampling:
Serum gastrin levels were measured by radioimmunoassay (RIA) using blood obtained from subjects early in the morning before breakfast on three different days (Days 0, 8, and 9). Urine was collected over 24 hours (from 08:00 to 08:00 the next day) on Days 0 and 7, and urinary gastrin excretion was determined using RIA to measure gastrin N-terminal fragments.

Safety:
Assessed by adverse events and clinical laboratory tests.

Statistical Methods:
Data were analyzed for 7 subjects during RBP administration and 8 subjects during OMP administration. The data for one subject during RBP administration were discarded because day 0 measurements were not made due to breakage of the glass electrode.

The pH 3 holding times (sum of the time during which pH $\geq$ 3) were calculated from the pH data. The pH 3 holding times for four 6 hour intervals (08:00 to 14:00, 14:00 to 20:00, 20:00 to 02:00, and 02:00 to 08:00) were also analyzed in order to clarify any time-dependent changes in gastric pH levels. The percent increases in the 24-hour pH 3 holding times from Day 0 to Days 6-7, and the percent decrease in the 24-hour pH 3 holding times from Days 6-7 to Day 8 were calculated. Data were analyzed using a t-test ($p < 0.05$).

Mean serum gastrin levels at the time of blood sampling were calculated for both RBP and OMP. Data was compared and analyzed using a t-test. Mean urinary gastrin excretion values before and after administration of study drugs were compared and analyzed using a t-test ($p < 0.05$).

RESULTS
Pharmacodynamics:
The percent increases in pH 3 holding times from Day 0 to Days 6-7 were greater during RBP administration than during OMP administration, however, the differences between the two drugs were not statistically significant due to large fluctuations in the data. The highest pH 3 holding times for both drugs occurred during the 14:00 to 20:00 interval. The pH 3 holding times for both drugs observed on Day 8 were lower than those for Days 6-7. The percent decrease in pH 3 holding times from Days 6-7 to Day 8 was greater during RBP than OMP administration, although the difference was not statistically significant. This was attributed to a recovery in gastric acid secretion to the extent that serum gastrin levels were no longer induced. Table 1 displays the mean changes in gastric pH 3 holding times for the 24-hour monitoring period and for each of the individual 6-hour time intervals.

APPEARS THIS WAY
ON ORIGINAL

Table 1. Changes (minutes) in pH 3 holding times (means±SD).

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

[a] the % increase in 24-hour pH 3 holding time compared to Day 0
[b] the % decrease in 24-hour pH 3 holding time compared to Days 6-7
Note: the % increases and decreases were calculated by this reviewer as the values submitted by the sponsor appeared to be in error

On Day 8, serum gastrin levels were statistically significantly elevated compared to Day 0 for both drugs. On Day 9, serum gastrin levels for both drugs had decreased to levels, which were close to and not significantly different from, the Day 0 levels. There were no significant differences between the two drugs. Table 2 displays the mean serum gastrin levels for each group.

Table 2. Mean (±SD) serum gastrin[a] levels (pg/ml).

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

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

Urinary gastrin excretion after drug administration was statistically significantly higher than before administration for both drugs. However, there were no significant differences between RBP and OMP.

Safety: No adverse events nor other abnormal findings were observed.

CONCLUSIONS:
The results illustrated that both RBP and OMP elicited pronounced increases in pH 3 holding time for the 24-hour period from Days 6-7 when compared to baseline values (Day 0). The greatest increases in this parameter occurred during the 14:00 to 20:00 interval. In addition, decreases in pH 3 holding times were observed on Day 8 (24 hours after the final dose) for both drugs, suggesting a recovery of gastric acid secretion.

The expected increases in serum gastrin levels, as a result of gastric acid suppression, were observed even though levels were not determined during drug administration. Reduction of serum gastrin levels from Day 8 to Day 9 was attributed to a recovery in gastric acid secretion. Likewise, the increase in excretion of urinary gastrin was attributed to the marked elevation of gastric pH resulting from the administration of study drugs.

Overall, administration of both RBP and OMP for 7 days resulted in significant gastric acid suppression. Furthermore, there were no statistically significant differences between the two drugs with respect to the parameters evaluated in this study.

REVIEWER'S COMMENTS:
1. No information was provided for subject demographics.
2. Very limited safety information was provided.
3. No individual or raw data (including pH readings) were provided in the study report.

APPEARS THIS WAY
ON ORIGINAL

TITLE: A trial to assess the effect of E3810 (rabeprazole sodium) on endocrine function and gastric secretory function in young healthy male Caucasian subjects.

Protocol Number: E3810-E044-106

Study Dates: August-October 1995

OBJECTIVE: to determine the effect of RBP on endocrine function and gastric secretory function in young healthy male subjects.

METHODS:
Study Design: single center, double-blind, randomized, placebo-controlled, crossover study

Study Population: 12 healthy, adult, male, Caucasian volunteers

Treatment and Administration:
Treatment 1: 20 mg RBP at 08:00 each morning before breakfast, daily for 14 days
Treatment 2: placebo at 08:00 each morning before breakfast, daily for 14 days
Subjects received the alternate treatment after a washout period of at least 7 days.

Gastric pH was monitored as follows:
1. over a 6-hour period from 00:00 to 06:00 on the morning of Day 7 (nocturnal pH)
2. for 24 hours from 08:00 on Day 7 to 08:00 on Day 8
3. for 72 hours from Days 14 to 17

Standard meals were provided throughout the study (timing of meals was not specified).

Drug Supplies:
20 mg enteric-coated RBP tablets; #K43017ZZA. *This is the to-be-marketed formulation.*
20 mg placebo tablets; K4Y002ZZC.

Pharmacodynamic Sampling/Analysis:
Gastric pH was measured using a glass electrode placed in the fundus of the stomach 10 cm below the gastroesophageal junction. The contents of the stomach were aspirated 4 times per hour through a nasogastric tube and 24-hour gastric acidity was calculated using the pH measurements obtained.

A 24-hour intragastric acidity profile was obtained on Days 7, 14, 15, and 16 for each subject and the AUC_{08-08} calculated. In addition, the intragastric acidity data were divided into four meal-related intervals: morning from 08:00 to 13:00, afternoon from 13:00 to 19:00, evening from 19:00 to 22:00, and night from 22:00 to 08:00. Corresponding AUCs were also calculated (AUC_{08-13}, AUC_{13-19}, AUC_{19-22} and AUC_{22-08}).

Endocrine Function:
Primary Endocrine Function: assessed by serum testosterone and circadian cortisol profiles pre-treatment and Day 13 of each treatment, 2 hours post-dosing. ACTH-stimulated cortisol profiles pre-treatment and Day 14 of each treatment.
Secondary Endocrine Function: Tri-iodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), thyroxine-binding protein (TBP), parathyroid hormone (PTH), insulin, glucagon, renin, follicle stimulating hormone (FSH), luteotrophic hormone (LH), prolactin, somatotrophic

hormone, aldosterone, dehydroepiandrosterone (DHEA), cortisol-binding globulin, and 17β-estradiol levels prior to treatment and on Day 13, 2 hours post-dosing. Urinary 6β-hydroxycortisol was measured prior to treatment and on Day 14.

Safety: Assessed via adverse events, vital signs, and clinical laboratory tests.

Statistical Methods:

All endocrine and antisecretory function data were summarized using descriptive statistics. Differences between the two treatments were assessed by ANOVA suitable for a two-period, cross-over study. All data processing, summarization, and analyses were performed using SAS for UNIX.

RESULTS:

Demographics:

One subject was discontinued from the study after completing the first treatment (RBP) due to intolerance of the nasogastric tube; his data was not included in the final data analysis. Per protocol, this subject was replaced and received the same sequence of treatments. All 12 subjects who completed the study were Caucasian with a mean age, height, and weight of 27.5 years, 180.9 cm, and 73.4 kg, respectively. Subjects included in the two sequence groups were comparable in demographic and baseline characteristics.

Primary Endocrine Function:

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

There were no significant differences in the circadian cortisol profile after 13 days of dosing with either RBP or placebo (Table 1). The baseline values, which were not included in the statistical analyses, were 16.2 ± 3.3, 11.6 ± 4.1, 5.2 ± 4.4, and 3.7 ± 2.0 μg/dL for 8 AM, 2 PM, 8 PM, and 2 AM, respectively. The baseline values were similar to the Day 13 values.

Table 1. Circadian Cortisol Profile (mean ± SD, μg/dL)

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

There were no significant differences in the cortisol levels after ACTH stimulation on the last day (Day 14) of RBP administration compared to placebo (Table 2). The baseline values, which were not included in the statistical comparison, were 15.2 ± 3.2, 23.1 ± 2.5 and 28.8 ± 3.0 μg/dL for pre-ACTH, 30 and 90 minutes, respectively. The baseline values were similar to the Day 14 values.

Table 2. ACTH-Stimulated Cortisol (mean ± SD, µg/dL)

Sampling Time Day 14	RBP 20 mg (N=12)	Placebo (N=12)	p-value (N=12)
Pre-ACTH	10.8 ± 2.9	10.7 ± 3.3	0.906
30 min post	21.0 ± 3.1	22.1 ± 4.0	0.472
90 min post	26.5 ± 3.5	27.2 ± 5.5	0.655

Other Endocrine Function:
Except for aldosterone, there were no statistically significant differences in the analyses of other measures of endocrine function after 13 days of RBP treatment compared to placebo. These other parameters included measures for thyroid and parathyroid function, glucose control, corticosteroid synthesis and reproductive hormones. The mean and standard deviation values for aldosterone were 83.9±34.4 pg/mL after RBP and 108.6±35.4 pg/mL after placebo (p = 0.02). However, this finding is unlikely to be clinically significant because there were no other changes in related parameters and the baseline value for aldosterone was 88.3±24.8 pg/mL, which is closer to the value after RBP treatment than the value after placebo treatment. In addition, all mean aldosterone values remained well within normal limits (40-310 pg/ml). Thus, the analysis of other measures of endocrine function did not reveal any clinically relevant effect of RBP.

Pharmacodynamics:
On Days 7 and 14 of treatment, the median intragastric pH was higher at each hourly measurement during RBP treatment (range, 3.92 to 6.88) than during placebo treatment (range, 1.48 to 4.22), indicating RBP caused a substantial increase in intragastric pH. On Days 15 and 16, which were the first two days after the cessation of treatment, the median pH for the RBP-treated subjects was still higher than the median pH for the placebo subjects at most measurement times, but the overall difference was smaller, indicating a partial return to pretreatment pH values. Figure 1 displays the median intragastric pH values for each study day after both RBP and placebo treatment.

The H^+ concentration was calculated from the pH, and the intragastric acidity was determined by integration of the H^+ concentration over 24 hours and for 4 meal-related intervals as described. For Days 7 and 14 of treatment and the first two days post-treatment, the intragastric acidity was significantly lower for RBP treatment than placebo treatment for the 24-hr period and all 4 meal-related intervals. After 14 days of dosing, RBP reduced the 24-hour integrated intragastric acidity by 87% compared to placebo treatment. Although still significantly less than placebo, the intragastric acidity after RBP treatment on Days 15 and 16 was higher compared to Days 7 and 14, indicating a partial recovery of gastric acid secretion. Mean intragastric acidity values are provided in Table 3 below.

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Table 3. Summary of Mean±SD Intragastric Acidity (mmol/L/hr)

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

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

The 6-hr nocturnal gastric acid secretion, measured between Days 7 and 8, was significantly lower (p<0.001) for RBP treatment (5.6±6.5 mmol/L) than for placebo (35.9±19.4 mmol/L), indicating substantial suppression of nocturnal gastric acid secretion by RBP.

Safety:
There were no deaths nor serious adverse events. Mild or moderate adverse events were reported by 5 of 12 (42%) subjects during placebo treatment and 8 of 13 (62%) subjects during RBP treatment. No clinically important differences between the two treatments were noted for any of the clinical laboratory or vital signs measurements.

CONCLUSIONS:
This study demonstrated the following results in healthy male adult volunteers who received daily doses of 20 mg RBP and placebo, each for 14 days:
- Treatment with RBP did not result in any clinically significant effects on serum testosterone levels, circadian serum cortisol profiles, ACTH-stimulated serum cortisol levels, or 17 other measures of endocrine function when compared with placebo treatment.
- Treatment with RBP substantially increased median intragastric pH over a 24-hour period after 7 and 14 days of dosing, and maintained higher pH values for at least 72 hours following the final dose, when compared to placebo.
- RBP treatment statistically significantly decreased intragastric acidity and nocturnal gastric acid secretion compared with placebo during all of the time intervals on all of the Days examined in this study.
- RBP 20 mg qAM was well tolerated when compared with placebo treatment.

STUDY #E044-106
Figure 1.
Median Intragastric pH Values by Study Day

Day 7

Day 14

Day 15

Day 16

Placebo — ▲ — 20 mg QAM
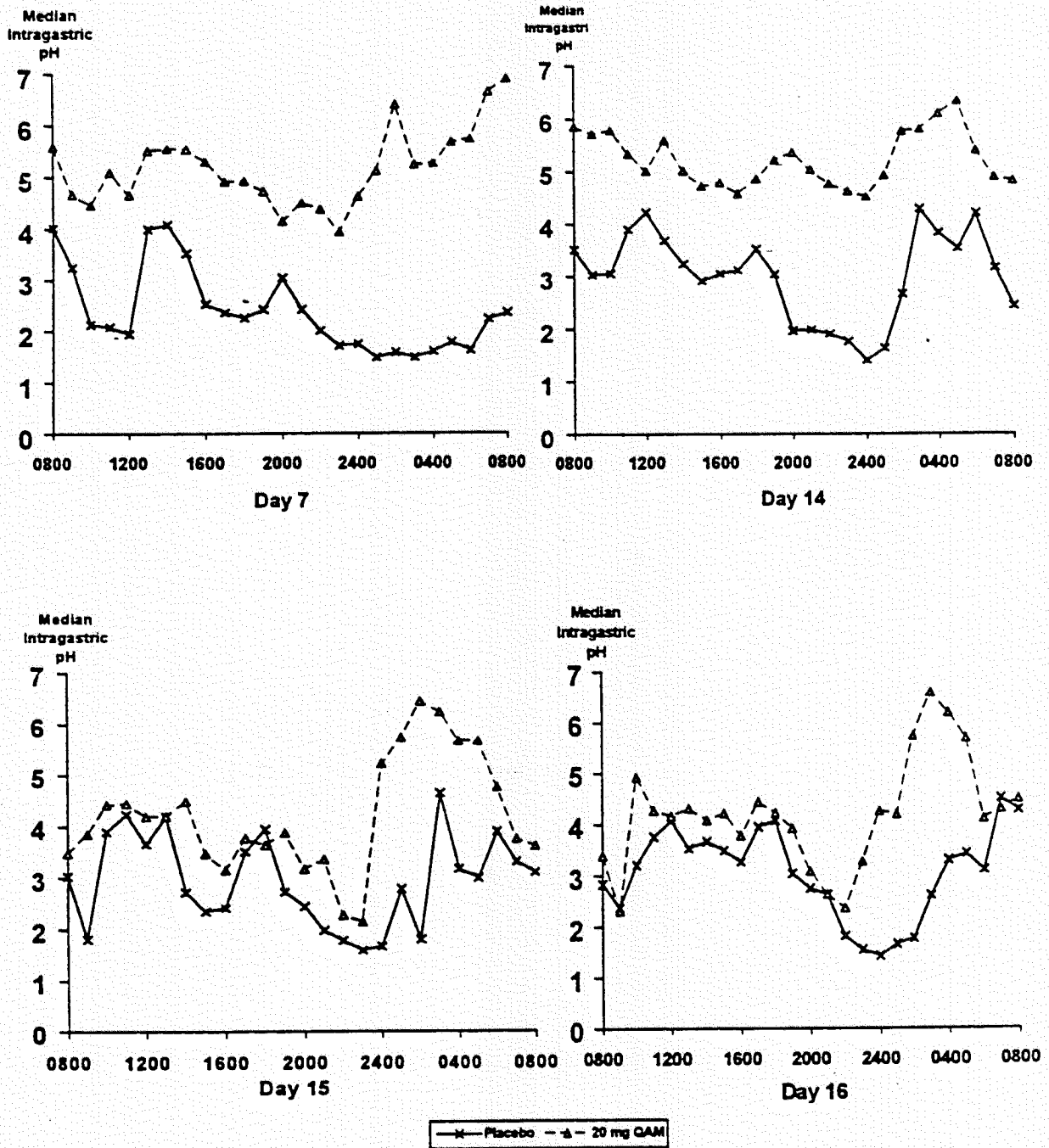
TITLE: A trial to assess the effect of seven-day dosing of rabeprazole on 24-hour intragastric acidity and plasma gastrin concentrations in young, healthy, male subjects

Protocol Number: E3810-E044-107

Study Dates: September-November 1995

OBJECTIVES:
1. to determine the dose-response relationship of RBP at steady-state.
2. to determine the effect of RBP on 24-hour intragastric acidity and plasma gastrin levels.

Study Design:
single-center, double-blind, randomized, placebo-controlled, four-period crossover

Population: 24 healthy, adult, male volunteers

Treatment and Drug Administration:
Sequences of RBP and placebo treatments were as follows:
Sequence 1 (6 subjects): 40 mg, placebo, 20 mg, 10 mg; each for 7 days
Sequence 2 (6 subjects): 10 mg, 20 mg, placebo, 40 mg; each for 7 days
Sequence 3 (6 subjects): 20 mg, 40 mg, 10 mg, placebo; each for 7 days
Sequence 4 (6 subjects): placebo, 10 mg, 40 mg, 20 mg; each for 7 days

There was a washout period of 7 days between treatment periods. RBP was administered orally in the fasting state at 8:00 AM before breakfast.

Drug Supplies:
10 mg enteric-coated RBP tablets; #K43019ZZA. *This was not the to-be-marketed formulation or strength.*
20 mg enteric-coated RBP tablets; #K48007ZZB. *This is the to-be-marketed formulation.*
10 mg placebo tablets; #K46013ZZB.
20 mg placebo tablets; #K4Y002ZZC and #K2Y022ZZD.

Pharmacodynamic Sampling:
Gastric Secretory Function: 24-hr intragastric pH and acidity from 8:00 AM Day 7 to 8:00 AM Day 8.
Plasma Gastrin Levels: hourly from 8:00 AM to 24:00 on Day 7 and every other hour from 0:00 to 8:00 AM on Day 8 (24 hours total).

Pharmacodynamic Analysis:
Intragastric acidity = (1/antilog pH)x 1000, where the antilog was calculated to the base 10.
A 24-hour intragastric acidity and plasma gastrin concentration was obtained for each subject and the AUC_{08-08} for each profile determined. The PD data was also separated into 4 meal-related intervals (morning/08:00-13:00, afternoon/13:00-19:00, evening/19:00-22:00, and night/22:00-08:00), and the partially integrated AUCs were calculated for each interval (AUC_{08-13}, AUC_{13-19}, AUC_{19-22}, and AUC_{22-08}). The exact timing of meals was as follows: breakfast at 08:15, snack at 10:45, lunch at 13:15, tea at 15:45, dinner at 18:15, and snack at 21:45.

Safety: Assessed by adverse events, vital signs, and clinical laboratory tests.

Statistical Methods:
PD parameters were summarized with descriptive statistics. Differences among treatments for the total and partial AUCs were assessed by an ANOVA model suitable for a four-way crossover study. Dose-response effects were assessed using an ANOVA model as well.

Analytical Methods:
Gastric Secretory Function: A [____] sump nasogastric tube was passed through each subject's nose into the stomach and small aliquots (5 ml) of gastric contents were aspirated on an hourly basis. The pH of each aliquot was immediately measured to the nearest 0.01 pH unit by means of a glass electrode and digital pH meter.
Serum gastrin - [____] No assay information was provided.

RESULTS:
Demographics:
All 24 subjects completed the study and were comparable in baseline characteristics, including height, weight, and age. Mean age, height, and weight for all subjects was 23.6 years, 178.6 cm, and 75 kg, respectively. The majority (19/24) were Caucasian while 4/24 were Western Asian and 1/24 was classified as other.

Pharmacodynamics:
At each hour for a 24-hour period after the last dose, the mean intragastric pH was higher after 7 days of treatment with 10, 20, or 40 mg RBP, than after 7 days of treatment with placebo. There was one individual who had lower intragastric pH reported after all three doses of RBP when compared to placebo during the 22:00-08:00 interval, however, his placebo AUC during this time was substantially greater than all of the other subjects.

Table 1 provides the mean±SD intragastric acidity data for each AUC interval during the different treatments. Median values are given in parentheses. At all time intervals for AUC on Day 7, the intragastric acidity was statistically significantly lower for all doses of RBP compared to placebo (p<0.001), indicating a significant effect of RBP on gastric acidity at steady-state. The reduction in 24-hour gastric acidity was 77%, 81%, and 87% in subjects who received 10, 20, and 40 mg of RBP, respectively. There were no statistically significant differences between dose levels of rabeprazole (p > 0.050) on this parameter, although there was a trend for a difference between the 10 mg vs the 40 mg dose (p=0.07) for the AUC_{08-08}.

Table 1. Mean±SD (medians) Intragastric Acidity AUC Data for Day 7 (mmol*hr/L).

AUC interval (hrs)	Treatment			
	10 mg RBP (N=24)	20 mg RBP (N=24)	40 mg RBP (N=24)	Placebo (N=24)
08:00 - 13:00	19.6±21.5 (16.4)	12.9±23 (2.8)	7.6±14.7 (0.7)	91.1±39.7 (84)
13:00 - 19:00	5.6±9.7 (0.7)	8.3±29.8 (0.2)	1.3±5.2 (0.1)	95.5±48.7 (85.1)
19:00 - 22:00	0.1±0.1 (0.0)	0.1±0.1 (0.0)	0.0±0.02 (0.0)	11.9±12.5 (5.9)
22:00 - 08:00	129.2±84 (120.2)	109.6±67.2 (95)	76.9±58.4 (75.7)	479.9±165 (483.3)
08:00 - 08:00	155.5±90.6 (186.2)	130.9±81 (129)	85.8±64.3 (81.7)	678.5±214 (696.9)

Plasma Gastrin:
Table 2 provides the plasma gastrin results for the different treatments during each AUC interval. At all time intervals for AUC on Day 7, the plasma gastrin was statistically significantly higher for all doses of RBP compared to placebo ($p < 0.001$). AUC values for the 40 mg RBP dose were significantly higher than the values for the 10 mg dose for all integration intervals, and higher than the 24-hr AUC value for 20 mg RBP. The p-values for individual time intervals for the 40 mg vs the 20 mg doses ranged from 0.040 to 0.082. There were no statistically significant differences between 10 mg and 20 mg RBP ($p \geq 0.102$). These results indicate that a 40 mg RBP dose elevates the plasma gastrin to a greater extent than the lower doses of 10 and 20 mg.

Table 2. Mean±SD Plasma Gastrin AUCs on Day 7 (pmol*hr/L).

AUC interval (hrs)	Treatment			
	10 mg (N=24)	20 mg (N=24)	40 mg (N=24)	Placebo (N=24)
08:00 - 13:00	258.7±234.8	308.3±244.9[a]	383.9±306.5[b,c]	52.2±59.4
13:00 - 19:00	570.9±461.1	644.1±456.5[a]	797.6±578.6[b,d]	100.2±127.6
19:00 - 22:00	336.7±234.6	409.1±304.7[a]	486.3±344.1[b,c]	74.3±91.6
22:00 - 08:00	459.3±410.4	523.7±475.8[a]	664.2±540.7[b,c]	64.1±75.2
08:00 - 08:00	1625.7±1312.7	1885.3±1429.3[a]	2332±1729.8[b,d]	290.8±346.3

[a] $p \geq 0.102$ for 10 mg vs 20 mg
[b] $p \leq 0.005$ for 10 mg vs 40 mg
[c] $p > 0.05$ for 20 mg vs 40 mg
[d] $p < 0.05$ for 20 mg vs 40 mg

Safety:
There were no deaths, serious adverse events or withdrawals from the study. Adverse events reported for three or more subjects at any one dose level were flatulence, headache, diarrhea and pharyngitis. The events judged to be severe by the investigator were diarrhea and vomiting for one subject who received 10 mg RBP, diarrhea for one subject who received 20 mg RBP, and headache and flatulence for two subjects who received 40 mg RBP. All other adverse events were judged to be mild or moderate in nature. No clinically important differences among the four dose levels were observed for clinical laboratory values or vital signs.

CONCLUSIONS:
This study revealed that, in comparison to placebo, RBP, administered at daily doses of 10 mg, 20 mg, and 40 mg QAM for 7 days to healthy young male subjects:
- Substantially increased intragastric pH after 7 days of dosing.
- Statistically significantly inhibited intragastric acidity. Reductions in mean integrated 24-hour intragastric acidity of 77%, 81%, and 87% were observed after the 10 mg, 20 mg, and 40 mg RBP doses, respectively, compared to placebo.
- Statistically significantly increased plasma gastrin levels. The 40 mg RBP dose elevated the plasma gastrin levels to a greater extent than the 10 mg and 20 mg doses.
- Displayed no substantial advantage at a dose of 40 mg vs 10 mg or 20 mg with respect to inhibition of intragastric acidity. Although the data suggested a dose-related trend in inhibition of gastric acidity, no statistically significant differences in AUCs were found among the three doses of active drug at any of the time intervals.
- May have a possible disadvantage at a dose of 40 mg vs 10 mg or 20 mg with respect to elevations in plasma gastrin concentration.
- Was generally well tolerated.

TITLE: A Placebo Controlled Trial to Assess the Effect of Eight Day Dosing of Rabeprazole versus Omeprazole on the 24-Hour Intragastric Acidity and Plasma Gastrin Concentrations in Young Healthy Male Subjects

Protocol Number: E3810-E044-115

Study Dates: September-November 1996

OBJECTIVES: to compare the effect of RBP, OMP, and placebo on 24-hour intragastric acidity and plasma gastrin concentrations.

METHODS:
Study Design: single-center, double-blind, placebo-controlled, randomized, three-way crossover

Study Population:
24 healthy males, aged 18 to 35 years, who tested *Helicobacter pylori*-negative

Treatment and Administration:
The 24 subjects were randonly assigned to the following treatments:
- 20 mg RBP; N=8
- 20 mg OMP; N=8
- Placebo; N=8

Subjects were dosed in the fasting state at 8:00 AM on each treatment day. The length of each dosing interval was eight days; subjects were crossed over so that they received all three treatments. Each dosing interval was separated by a washout period of one week.

Intragastric pH was monitored from 08:00 hours on Day 1 to 08:00 hours on Day 2, and from 08:00 hours on Day 8 to 08:00 hours on Day 9. Standard meals were provided on Days 1 and 8 and consisted of breakfast (08:15), mid-morning snack (10:45), lunch (13:15), afternoon snack 15:45), dinner (18:15), and evening snack (21:45).

Study drug supplies:
20 mg enteric-coated RBP tablet; #K5Y006ZZB. *This is the to-be-marketed formulation.*
Placebo tablets (matching RBP); #K63008ZZA
20 mg OMP capsule; #PO380A
Placebo capsules (matching OMP); #PO380B

Pharmacodynamic Sampling/Analysis:
A nasogastric tube was passed into the stomach and small aliquots of gastric contents were aspirated on an hourly basis. The pH of the fluid was measured immediately by means of a glass electrode and digital pH meter. The primary pharmacodynamic assessment for this study was a 24-hour profile of intragastric acidity on Day 1 and Day 8 of each dosing period, which was calculated using a standard conversion formula from the hourly pH measurements. In addition, on Day 8 of each dosing period, 24-hour plasma gastrin concentrations were determined by RIA.

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