Impact of Increased Gastric pH on the Pharmacokinetics of Evacetrapib in Healthy Subjects

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Study Objective To examine the effect of increased gastric pH on exposure to evacetrapib, a cholesteryl ester transfer protein inhibitor evaluated for the treatment of atherosclerotic heart disease.

Design Open-label, two-treatment, two-period, fixed-sequence crossover study.

Setting Clinical research unit.

Subjects Thirty-four healthy subjects.

Intervention In period 1, subjects received a single oral dose of evacetrapib 130 mg on day 1, followed by 7 days of analysis for evacetrapib plasma concentrations. In period 2, subjects received a once/day oral dose of omeprazole 40 mg on days 8–20, with a single oral dose of evacetrapib 130 mg administered 2 hours after the omeprazole dose on day 14, followed by 7 days of pharmacokinetic sampling. Subjects were discharged on day 21 and returned for a follow-up visit at least 14 days after the last dose of evacetrapib in period 2. Gastric pH was measured before subjects received each evacetrapib dose.

Measurements and Main Results Noncompartmental pharmacokinetic parameters were estimated from plasma concentration–time data and compared between periods 1 and 2. Geometric mean ratios with 90% confidence intervals (CIs) were reported. Safety and tolerability were also assessed. The mean age of the 34 subjects was 40.9 years; mean body mass index was 27.2 kg/m^2. Omeprazole treatment increased mean gastric pH across all subjects by 2.80 and increased evacetrapib area under the concentration versus time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$) and maximum observed drug concentration (C_{max}) by 15% (90% CI −2 to 35) and 30% (90% CI 3–63), respectively. For both parameters, the upper bound of the 90% CI of the ratio of geometric least-squares means exceeded 1.25 but was less than 2, indicating a weak interaction. To assess the effect of gastric pH on subjects who responded best to omeprazole treatment, the analyses were repeated to include only the 22 subjects whose predose gastric pH was 3.0 or lower in period 1 and 4.0 or higher in period 2. In this subpopulation, mean gastric pH increased by 4.15 during omeprazole treatment, and evacetrapib $AUC_{0-\infty}$ and C_{max} increased by 22% (90% CI 4–42) and 35% (90% CI 1–80), respectively. Despite the small mathematical differences between the analyses, the overall effect in both was a minimal increase in evacetrapib exposure. Of 35 adverse events reported during the study, 4 (11.4%) were considered to be treatment-related, and most were mild in severity.

Conclusion The impact of increased gastric pH on evacetrapib pharmacokinetics would not be expected to be clinically relevant. The magnitude of change in pH did not affect the degree of the interaction.

Key Words evacetrapib, omeprazole, gastric pH, pharmacokinetics.

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Although aggressive lowering of low-density lipoprotein cholesterol (LDL-C) is beneficial in lowering cardiovascular events,[1] therapies are still needed to target other lipid-related risk factors to address residual cardiovascular disease. Significant efforts have focused on the development of novel therapeutic agents designed to address this unmet need.

Epidemiologic evidence indicates that high-density lipoprotein cholesterol (HDL-C) levels are inversely correlated with cardiovascular disease risk,[2, 3] suggesting that agents that raise HDL-C levels may offer important benefits in treating cardiovascular disease.

Compounds that inhibit cholesteryl ester transfer protein (CETP) can increase HDL-C levels and may provide favorable benefits toward lowering cardiovascular risk.[4–6] Evacetrapib, a potent and selective inhibitor of CETP, demonstrated its ability to increase HDL-C and decrease LDL-C levels and was hypothesized to reduce the risk of major adverse cardiovascular events in patients with high-risk vascular disease.[7–10] On October 12, 2015, however, Eli Lilly and Company announced the termination of its phase III evacetrapib trial due to insufficient efficacy following a recommendation by the independent data monitoring committee (https://investor.lilly.com/releasedetail.cfm?relea seid=936130).

The intended patient population for evacetrapib potentially included those taking proton pump inhibitors, such as omeprazole, for the treatment of gastrointestinal ulcers and gastric reflux. Omeprazole inhibits gastric acid secretion and thereby increases the pH of the gastric environment, which may alter the absorption of drugs with pH-dependent solubility.[11] Omeprazole is a potent inhibitor of cytochrome P450 (CYP) 2C19, but there is no drug–drug interaction risk with evacetrapib because its clearance is mediated by CYP3A and CYP2C8, and not CYP2C19.[12] Oral dosing with omeprazole once/day achieves maximum suppression of gastric acid secretion within ~4 days of treatment. After dosing with omeprazole 40 mg once/day for 7 days, median 24-hour gastric pH was increased in healthy subjects from 1.68 to 4.93, with the largest increases in gastric pH occurring 2–10 hours after the omeprazole dose.[13]

The current study examined the impact of increased gastric pH on systemic exposure to evacetrapib, whose solubility is pH dependent. The results of gastric pH evaluations and the pharmacokinetics, safety, and tolerability of a single oral dose of evacetrapib 130 mg given alone and with omeprazole are presented. The treatment of healthy subjects with omeprazole likened the gastric environment to that of conditions similar to others with achlorhydria (Table S1). Although evacetrapib development has been discontinued, the methods and analyses described in this study may be relevant to researchers wanting to conduct gastric pH–drug interaction studies with other drug candidates.

Methods

Study Design and Treatment Protocol

This was an open-label, two-treatment, two-period, fixed-sequence crossover study evaluating the effect of increased gastric pH on the pharmacokinetics of evacetrapib in healthy human subjects. Each subject participated in a screening visit, two dosing periods, and a post-study follow-up visit. Subjects were admitted to the clinical research unit on day 1 and remained resident until completion of period 2. In period 1, subjects received a single oral dose of evacetrapib 130 mg on day 1 followed by 7 days of pharmacokinetic sampling. In period 2, an oral dose of omeprazole 40 mg (Kremers Urban Pharmaceuticals, Inc., Princeton, NJ) was administered once/day on days 8–20, with a single oral dose of evacetrapib 130 mg administered 2 hours after the omeprazole dose on day 14. Omeprazole 20 mg/day achieves maximal acid suppression within ~4 days,[11] and the effect of a 40-mg dose was expected to follow a similar time course. Therefore, the second dose of

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evacetrapib was administered 6 days after the first omeprazole dose to ensure that subjects had attained maximal suppression of gastric acid secretion. Subjects were discharged on day 21 and returned for a follow-up visit at least 14 days after the last dose of evacetrapib in period 2.

Subjects

Eligible subjects included healthy men and women not of childbearing potential, 18–65 years of age, with a body mass index of 18.0–32.0 kg/m^2. Use of over-the-counter or prescription medication was prohibited within 14 days prior to dosing and during the study, with the exception of occasional acetaminophen use.

All subjects provided written informed consent before beginning any study procedures. The study protocol was approved by the institutional review board (Schulman Associates Institutional Review Board, Inc., Cincinnati, OH) and was conducted in accordance with regulatory guidances and good clinical practice guidelines.

Gastric pH Evaluations

The ZepHr Impedance/pH Reflux Monitoring System with AirFLOW Sphincter Locator (Sandhill Scientific, Highlands Ranch, CO) and corresponding ComforTec PLUS single-use infused 2.3-mm pH probes (Sandhill Scientific) were used to test the pH of the gastric environment. The ZepHr recorder was set up and calibrated according to the manufacturer's instructions. Then the recorder and probe were connected to the AirFLOW Sphincter Locator, and the sphincter locator was pumped up to ~7.5 psi. The nasogastric probe was then inserted to ~60 cm so that the probe's infusion port was below the lower esophageal sphincter (LES) and in the stomach. Pressure on the recorder screen was set to zero. The probe was then pulled back in 1-cm increments while observing the pressure and pH on the recorder screen. As the locator infusion port entered the LES, there would be an increase in pressure to a two-digit positive number. After identifying the high pressure of the LES, the probe was advanced ~5 cm so the pH sensor was positioned ~10 cm below the LES. The probe was taped in position, and pH was recorded for ~15 minutes prior to administration of evacetrapib on days 1 and 14.

Bioanalysis and Pharmacokinetic Assessments

Blood samples were collected for pharmacokinetic analysis of evacetrapib before and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours after the evacetrapib doses were given on days 1 and 14. Plasma samples were analyzed for evacetrapib by using a validated liquid chromatography with the tandem mass spectrometric method at Covance Laboratories Inc. (Madison, WI). The lower and upper limits of quantification were 1.00 and 1000 ng/ml, respectively. The interassay accuracy, defined as the closeness of the mean value obtained by the method to the actual nominal value of the analyte and expressed as a percent, ranged from −2.9 to 1.5% during validation. The interassay precision, defined as the closeness of repeated individual measures of the analyte and expressed as the coefficient of variation, ranged from 2.9 to 6.4% during validation. Both precision and accuracy measures met the predefined acceptance criteria consistent with regulatory guidances,[14, 15] thus confirming the robustness of the bioanalytical assay.

The potential for omeprazole to interfere with evacetrapib in the bioanalytical assay was assessed at an omeprazole concentration of 650 ng/ml. There was no significant interference in the chromatographic regions of interest for evacetrapib, indicating that the evacetrapib method had acceptable selectivity in the presence of omeprazole.

Pharmacokinetic parameter estimates for evacetrapib were calculated by using standard noncompartmental methods of analysis using WinNonlin software, v.6.2.1 (Pharsight Corp., Mountain View, CA). The primary parameters for analysis were area under the concentration versus time curve (AUC) from time zero to the last time point with a measurable concentration ($AUC_{0–tlast}$); AUC from time zero extrapolated to infinity ($AUC_{0–\infty}$); maximum observed drug concentration (C_{max}); and the time to reach maximum concentration (T_{max}). The AUC was calculated by using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method was applied up to T_{max}, and then the logarithmic trapezoidal method was used after T_{max}. The minimum requirement for the calculation of AUC was the inclusion of at least three consecutive plasma concentrations above the lower level of quantitation, with at least one of these concentrations following C_{max}. The C_{max} and T_{max} were reported from visual inspection of the concentration versus time

curve. The apparent terminal elimination half-life ($t_{1/2}$), apparent clearance, and apparent volume of distribution during the terminal phase were also estimated. The $t_{1/2}$ was calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration–time curve. The start of the terminal elimination phase for each subject was determined by visual inspection and generally was the first point at which there was no systematic deviation from the log-linear decline in plasma concentrations. The $t_{1/2}$ was estimated only when at least three concentrations were available for its calculation in the terminal phase. Descriptive statistics, including geometric mean and coefficient of variation (CV), were calculated.

Safety Assessments

Safety was assessed by monitoring treatment-emergent adverse events, physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), and clinical laboratory evaluations. Clinical laboratory safety parameters included hematology, urinalysis, and biochemistry panels.

Statistical Analysis

Sample Size

The sample size was based on a calculation of precision of the estimated $AUC_{0-\infty}$. Using an intrasubject variability estimate of 36.5% for evacetrapib (ClinicalTrials.gov identifier NCT 01903434; data on file),[16] a sample size of 30 subjects completing the trial provided ~90% coverage probability that the half-width of the 90% CI for the ratio of geometric mean $AUC_{0-\infty}$ was within 0.18 in the log scale, which corresponded to ~20% in the natural scale.

Pharmacokinetic Analysis

The effects of gastric pH on evacetrapib $AUC_{0-\infty}$ and C_{max} were analyzed by using a mixed-effects analysis of variance model. Parameters were log-transformed prior to analysis. The model included a fixed effect for treatment (evacetrapib alone or evacetrapib + omeprazole) and a random effect for subject. The ratios of geometric least-squares (LS) means for evacetrapib + omeprazole (test treatment) compared with evacetrapib alone (reference treatment) were calculated along with the 90% CIs of the ratios. The ratios of geometric LS means were considered statistically significant if the 90% CIs did not contain 1. The T_{max} for evacetrapib was analyzed by using SAS procedure PROC UNIVARIATE software. The median of differences and ~90% CI for the median of differences between evacetrapib + omeprazole and evacetrapib alone were calculated. The difference in T_{max} was considered statistically significant if the 90% CI did not contain zero.

These analyses were repeated for subjects whose predose gastric pH was 3.0 or lower on day 1 and 4.0 or higher on day 14.

Results

Study Population

Thirty-four healthy subjects (30 male and 4 female), aged 22–61 years with a mean body mass index of 27.2 kg/m^2, entered the study and received at least one dose of evacetrapib. The enrolled subjects were white (19 subjects), black or African American (14 subjects), and Asian (1 subject). Thirty-two subjects completed the study; two subjects did not complete the study for the following reasons: one subject did not attend the follow-up visit after receiving all scheduled doses of evacetrapib and omeprazole, and one subject was discontinued due to an adverse event of hematuria that was considered unrelated to evacetrapib.

Gastric pH Measurements

Gastric pH was measured prior to evacetrapib administration alone on day 1 and on day 14 after omeprazole administration but before evacetrapib administration. Mean gastric pH for all subjects had increased by 2.80 (range −2.1 to 5.8) after 7 days of omeprazole treatment (Table 1). A subpopulation of 22 subjects had predose gastric pH of 3.0 or lower on day 1 and 4.0 or higher on day 14; mean gastric pH in this subpopulation had increased by 4.15 (range 1.9–5.8) after omeprazole treatment.

Pharmacokinetics

Figure 1A shows the mean plasma concentration–time profiles of evacetrapib given alone (day 1) and with omeprazole 40 mg once/day (day 14). Predose concentrations of evacetrapib were quantifiable for 14 of the 33 subjects in period 2 and were likely due to carry over from period 1. These concentrations ranged from 0.06 to 1.22% of C_{max} and were included in the analysis. Given

Table 1. Gastric pH Measurements Prior to a Single Dose of Evacetrapib 130 mg Administered Alone or with Omeprazole 40 mg Once/Day

	Gastric pH before evacetrapib 130 mg administered alone on day 1	Gastric pH before evacetrapib 130 mg administered with omeprazole 40 mg on day 14
All subjects	n=34	n=33
Mean ± SD	2.01 ± 0.98	4.81 ± 2.01
Range	1.2–6.1	1.3–7.4
Subjects with pH ≤ 3.0 on day 1 and ≥ 4.0 on day 14	n=22	n=22
Mean ± SD	1.80 ± 0.45	5.95 ± 0.91
Range	1.2–3.0	4.2–7.4

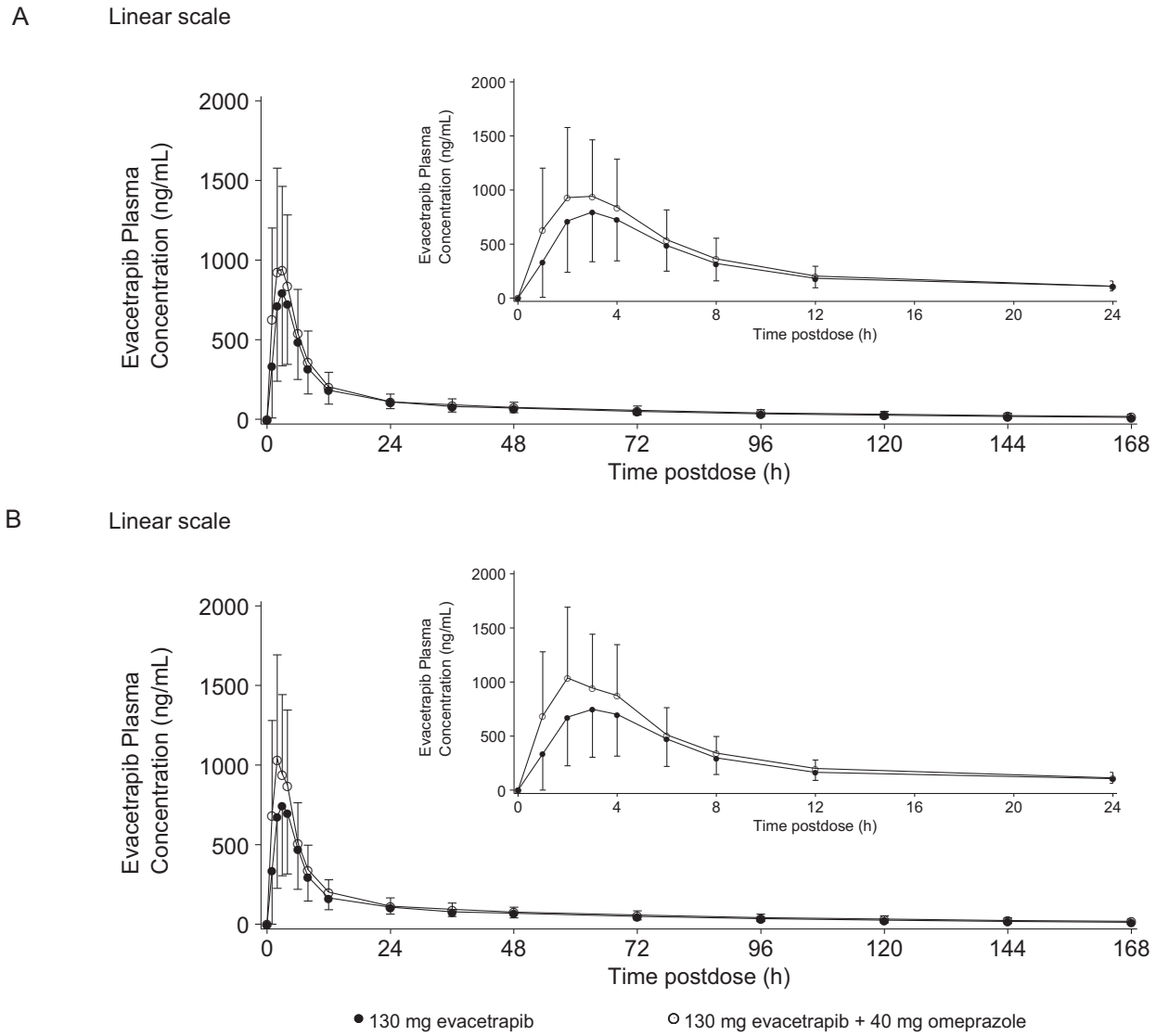

Figure 1. Arithmetic mean ± SD plasma concentration versus time profiles of evacetrapib following evacetrapib 130 mg given without omeprazole on day 1 (filled circles) and with omeprazole 40 mg once/day on day 14 (open circles). Panel A includes data from all subjects. Panel B includes data only from subjects whose predose gastric pH was 3.0 or lower on day 1 and 4.0 or higher on day 14. Insets show the data for 0–24 hours after evacetrapib dosing for better visualization of that interval.

the magnitude of these predose concentrations relative to postdose concentrations, their effect on AUC estimates was considered negligible.

Table 2 summarizes the geometric mean pharmacokinetic parameter estimates. Omeprazole treatment increased the geometric LS mean

$AUC_{0-\infty}$ and C_{max} of evacetrapib by 15% (90% CI −2 to 35) and 30% (90% CI 3–63), respectively (Table 3). The between-subject CV for $AUC_{0-\infty}$ was 40.9% (90% CI 30.8–63.3) and for C_{max} was 49.7% (90% CI 35.6–88.5). There was no statistically significant difference in T_{max} between the treatments.

The statistical analysis was repeated to include only the 22 subjects whose predose gastric pH was 3.0 or lower on day 1 and 4.0 or higher on day 14. The purpose of analyzing this subgroup was to assess the effect of increased gastric pH on subjects who responded best to omeprazole treatment, which represents a so-called worst case scenario for the effect of increased gastric pH on evacetrapib pharmacokinetics. Figure 1B shows the mean plasma concentration-time profiles for evacetrapib following evacetrapib 130 mg with and without omeprazole in this subgroup. Table 2 summarizes the geometric mean pharmacokinetic parameter estimates for this subgroup. In this subgroup, omeprazole treatment increased the geometric LS mean $AUC_{0-\infty}$ and C_{max} of evacetrapib by 22% (90% CI 4–42) and 35% (90% CI 1–80), respectively (Table 3). The subgroup's between-subject CV for $AUC_{0-\infty}$ was 50.7% (90% CI 38.2–78.8) and for C_{max} was 61.7% (90% CI 43.1–120). As in the analysis including all subjects, for both parameters the upper bound of the 90% CI of the ratio of geometric LS means exceeded 1.25 but was less than 2, and there was no statistically significant difference in T_{max} between the treatments.

Safety and Tolerability

The number of subjects reporting treatment-emergent adverse events was generally low across the treatment periods and was similar when evacetrapib was administered alone and with omeprazole. Thirty-five events were reported during the study, four (11.4%) of which were considered by the investigator to be treatment related. Following evacetrapib alone, two subjects each reported a headache, and one subject experienced a mild tremor. During administration of omeprazole alone, one subject reported constipation. Most events were mild in severity, except for three moderate events of furuncle, headache, and hematuria that were considered by the investigator to be related to other medical conditions. There were no clinically meaningful findings in safety assessments from clinical laboratory parameters, vital sign measurements, or 12-lead safety ECGs for individual subjects during the study that were considered related to the study drugs.

Discussion

This study determined the effect of increased gastric pH on the pharmacokinetics of evacetrapib in healthy subjects. Seven doses of omeprazole 40 mg once/day increased mean gastric pH values across all subjects by 2.80 and increased the geometric LS mean $AUC_{0-\infty}$ and C_{max} of evacetrapib by 15% and 30%, respectively. Given the range of the 90% CIs for $AUC_{0-\infty}$ and C_{max}, the magnitudes of these increases are comparable. For both

Table 2. Pharmacokinetic Parameter Estimates Following a Single Dose of Evacetrapib 130 mg Alone or with Omeprazole 40 mg Once/Day

	Geometric mean (CV%)			
	All subjects		Subjects with predose gastric pH ≤ 3.0 on day 1 and ≥ 4.0 on day 14	
Parameter	Evacetrapib 130 mg alone (n=34)	Evacetrapib 130 mg + omeprazole 40 mg (n=33)	Evacetrapib 130 mg alone (n=22)	Evacetrapib 130 mg + omeprazole 40 mg (n=22)
$AUC_{0-tlast}$, ng×hr/ml	11,700 (49)	13,000 (63)	11,200 (52)	13,400 (63)
$AUC_{0-\infty}$, ng×hr/ml	12,400 (52)	14,100 (66)	12,000 (55)	14,600 (67)
$\%AUC_{tlast-\infty}$, %	4.65 (95)	6.06 (95)	4.87 (94)	6.37 (82)
C_{max}, ng/ml	748 (79)	959 (88)	682 (89)	923 (98)
T_{max}[a], hrs	3.00 (2.00–6.00)	3.00 (1.00–6.00)	3.00 (2.00–6.00)	2.54 (1.00–6.00)
$t_{1/2}$[b], hrs	44.0 (26.9–80.6)	49.8 (27.1–87.6)	44.4 (26.9–80.6)	50.3 (27.6–87.6)
CL/F, L/hr	10.5 (52)	9.20 (66)	10.9 (55)	8.92 (67)
V_z/F, L	664 (45)	661 (49)	696 (44)	647 (46)

AUC = area under the concentration versus time curve; $AUC_{0-\infty}$ = AUC from time zero extrapolated to infinity; $AUC_{0-tlast}$ = AUC from time zero to the last time point with a measurable plasma concentration; $\%AUC_{tlast-\infty}$ = percentage of $AUC_{0-\infty}$ derived from extrapolation; CL/F = apparent clearance; C_{max} = maximum observed drug concentration; CV = coefficient of variation; $t_{1/2}$ = apparent terminal elimination half-life; T_{max} = time to reach C_{max}; V_z/F = apparent volume of distribution during the terminal phase.
[a]Data are median (range).
[b]Data are geometric mean (range).

Table 3. Statistical Analysis of Pharmacokinetic Parameter Estimates of Evacetrapib Following Evacetrapib 130 mg Administered Alone or with Omeprazole 40 mg Once/Day

		All subjects			Subjects with predose gastric pH ≤ 3.0 on day 1 and ≥ 4.0 on day 14		
Parameter	Treatment	No. of subjects	Geometric LS means	Ratio of geometric LS means (evacetrapib + omeprazole-to-evacetrapib; 90% CI)	No. of subjects	Geometric LS means	Ratio of geometric LS means (evacetrapib + omeprazole-to-evacetrapib; 90% CI)
$AUC_{0-\infty}$, ng×hr/ml	Evacetrapib	34	12,438		22	11,979	
	Evacetrapib + omeprazole	33	14,313	1.15 (0.982–1.35)	22	14,575	1.22 (1.04–1.42)
C_{max}, ng/ml	Evacetrapib	34	748		22	682	
	Evacetrapib + omeprazole	33	969	1.30 (1.03–1.63)	22	923	1.35 (1.01–1.80)

		All subjects			Subjects with predose gastric pH ≤ 3.0 on day 1 and ≥ 4.0 on day 14		
Parameter	Treatment	No. of subjects	Median	Median of differences (evacetrapib + omeprazole − evacetrapib; 90% CI)	No. of subjects	Median	Median of differences (evacetrapib + omeprazole − evacetrapib; 90% CI)
T_{max}, hrs[a]	Evacetrapib	33	3.00		22	3.00	
	Evacetrapib + omeprazole	33	3.00	0.00 (−1.00–0.00)	22	2.54	0.00 (−1.00–0.00)

$AUC_{0-\infty}$ = area under the concentration versus time curve from time zero extrapolated to infinity; CI = confidence interval; C_{max} = maximum observed drug concentration; LS = least squares; T_{max} = time to reach C_{max}.
Model: Log (PK) = Subject + Treatment + Random Error, where subject is fitted as a random effect.
[a]T_{max} analyzed nonparametrically by using SAS procedure PROC UNIVARIATE software.

pharmacokinetic parameters, the upper bound of the 90% CI of the ratio of geometric LS means exceeded 1.25 but was less than 2, indicating a weak interaction according to U.S. Food and Drug Administration guidance.[17]

The study's objective was to determine the effect of increased gastric pH on the pharmacokinetics of evacetrapib, not to determine the specific effect of concomitant omeprazole treatment on evacetrapib's pharmacokinetics. Omeprazole was the tool used to increase gastric pH, but because omeprazole did not accomplish this in every subject, it diluted the effect of omeprazole in the analysis across all subjects that included the subjects who did respond. To better evaluate the objective, given the poor response to omeprazole in some subjects, a subgroup analysis was conducted that included only the 22 subjects whose gastric pH was 3.0 or lower on day 1 and 4.0 or higher on day 14. By these criteria, each subject in the analysis had a pH increase of at least 1.0, and, in fact, the analysis included all subjects who had a pH increase of at least 1.0 except for one subject, whose pH increased from 6.1 at baseline to 7.3 on omeprazole. In this subpopulation, mean gastric pH increased by 4.15 during 7 days of omeprazole treatment, and geometric LS mean $AUC_{0-\infty}$ and C_{max} of evacetrapib increased by 22% and 35%, respectively. These increases were similar to the respective 15% and 30% increases across all subjects, which indicates that the analysis across all subjects was not significantly influenced by including subjects who did not respond well to omeprazole. Despite the small mathematical differences in the two analysis groups, the overall effect is a minimal increase in evacetrapib exposure.

Several steps were taken to determine accurate gastric pH measurements for individual subjects during the study. After positioning the probe using the AirFLOW Sphincter Locator, gastric pH measurements were collected using the ZepHr Monitoring System and averaged over 15 minutes. This system is used clinically for measuring pH in the lower esophagus during gastric reflux episodes, and it was adapted in this study to measure pH in the stomach. The ZepHr System uses a thin flexible probe that is more comfortable and less likely to coil compared with standard nasogastric tubes often used for monitoring gastric pH. To ensure that pH measurements were being collected in the stomach, a three-tiered approach was used to confirm placement of the probe. First, the sphincter locator allowed identification of increased pressure at the LES so that the pH probe could be positioned about 10 cm

below it, well into the stomach. Although positioning the pH probe using the AirFLOW Sphincter Locator takes slightly longer, it did not appear to cause additional discomfort to the subjects. Second, the pH gradient from the esophagus to the stomach was assessed on the recorder as the device was inserted. The pH gradient was most obvious in period 1 but was still present after 7 days of omeprazole administration in period 2. Lastly, the length of the pH probe at the nose was recorded for each subject at the time of pH recording in each period. The probe length at the nose after insertion in period 2 was compared with that of period 1 because this is unlikely to change significantly for individual subjects if the probe is placed similarly. Using these three methods to confirm proper placement into the stomach ensured that valid pH measurements were recorded for both periods.

Subjects were kept at the clinical research unit for the duration of the study to ensure compliance with study restrictions and dose administration. While in the clinical research unit, subjects were given standardized meals and were fasted prior to pH measurements and evacetrapib dosing to minimize any effect of dietary variations between treatments. The recommended dose of omeprazole 20 mg once/day achieves maximal acid suppression within about 4 days, and the 40-mg omeprazole dose used in this study was expected to have a similar effect. Therefore, the evacetrapib dose administered on day 14 after the seventh dose of omeprazole was given after maximal suppression of gastric acid secretion had been attained.

Conclusion

Increased gastric pH during treatment with omeprazole 40 mg once/day increased evacetrapib $AUC_{0-\infty}$ and C_{max} by 15% and 30%, respectively. For both parameters, the upper bound of the 90% CI of the ratio of geometric LS means exceeded 1.25 but was less than 2, indicating a weak interaction. The effect of increased gastric pH on evacetrapib pharmacokinetics would not be expected to be clinically relevant.

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Supporting Information

The following supporting information is available in the online version of this paper:

Table S1. Causes of Achlorhydria