

ARTICLE

Evaluation of the pharmacokinetics of trazpiroben (TAK-906) in the presence and absence of the proton pump inhibitor esomeprazole

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Funding information

This study was sponsored by Takeda Development Center Americas, Inc. Medical writing assistance was provided by Luke Bratton and Alexandra Kisbey-Ascott of Oxford PharmaGenesis, Oxford, UK and was supported by Takeda Development Center Americas, Inc.

Abstract

Trazpiroben, a dopamine D₂/D₃ receptor antagonist under development to treat gastroparesis, displays decreasing solubility with increasing pH. This single-sequence, open-label, two-period, crossover study evaluated the effect of esomeprazole, a proton pump inhibitor that raises gastric pH, on the single-dose pharmacokinetics, safety, and tolerability of trazpiroben in healthy adults (NCT03849690). In total, 12 participants were enrolled and entered period 1 (days 1–3), receiving a single oral dose of trazpiroben 25 mg on day 1. After a 4-day washout, participants then entered period 2 (days 8–13) and received esomeprazole 40 mg once daily on days 8–12, with a single oral dose of trazpiroben 25 mg co-administered 1 h post esomeprazole dosing on day 11. Geometric mean area under the curve from time 0 extrapolated to infinity (AUC_∞) and maximum plasma concentration (C_{max}) values were generally similar when trazpiroben was administered alone versus alongside esomeprazole (AUC_∞, 44.03 vs. 38.85 ng h/ml; C_{max}, 19.76 vs. 17.24 ng/ml). Additionally, the associated geometric mean ratio (GMR; co-administration: administration alone) 90% confidence intervals (CIs) suggested no clinically meaningful difference between treatment groups (AUC_∞, GMR 0.88, 90% CI 0.78–1.00; C_{max}, 0.87, 90% CI 0.70–1.09). Mean apparent first-order terminal elimination half-life values were similar between treatments, illustrating co-administration with esomeprazole had minimal effect on trazpiroben elimination. Trazpiroben was well-tolerated in healthy adults following administration alone and alongside esomeprazole, with no clinically relevant adverse events reported. The lack of evidence of any clinically meaningful drug–drug interaction supports the co-administration of esomeprazole with trazpiroben.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Gastroparesis is a gastric motility disorder typified by delayed gastric emptying without mechanical obstruction, with affected patients experiencing a range of gastrointestinal symptoms. Patients with gastroparesis may experience symptom overlap with, or comorbid, gastroesophageal reflux disease. Proton pump inhibitors (PPIs), which raise gastric pH, are frequently used to provide symptomatic relief. Trazpiroben is a dopamine D₂/D₃ receptor antagonist under development to treat gastroparesis. Given that trazpiroben displays decreasing solubility with increasing pH, the potential for a drug–drug interaction (DDI) with a PPI was evaluated.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study evaluated the effect of the PPI esomeprazole on the single-dose pharmacokinetics, safety, and tolerability of trazpiroben in healthy adults.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The results of this study demonstrated no evidence of any clinically meaningful DDI between trazpiroben and esomeprazole. Trazpiroben was well-tolerated following administration alone and alongside esomeprazole, with no clinically relevant adverse events reported.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The current treatment landscape for gastroparesis is limited, with use of available therapies restricted by safety concerns. Our findings support the potential co-administration of trazpiroben and esomeprazole, indicating that trazpiroben could represent a promising treatment option for patients with gastroparesis who are receiving PPI therapy.

INTRODUCTION

Gastroparesis is a gastric motility disorder that is characterized by delayed gastric emptying in the absence of mechanical obstruction.¹ Typical symptoms include early satiety, postprandial fullness, bloating, nausea, vomiting, and upper abdominal pain, which are chronic with episodes of exacerbation.^{1–4} In addition to these cardinal symptoms, patients with gastroparesis may also experience symptoms of gastroesophageal reflux, such as heartburn, regurgitation, and a bitter taste in the mouth.⁵ Gastroparesis is associated with a substantial health care burden,^{6,7} in addition to significantly impacting the patient's quality of life⁸ through disruption of daily activities and lowering of the patient's annual income.⁷

Currently, therapies for gastroparesis remain limited. Available treatment options include dietary modification, non-pharmacological interventions, such as endoscopic or surgical measures, gastric electrical stimulation, and anti-emetic or prokinetic medications for symptomatic disease management.^{9,10} Metoclopramide is a centrally penetrating dopamine D₂ receptor antagonist approved by the US Food and Drug Administration (FDA) for the symptomatic treatment of acute or recurrent diabetic gastroparesis.¹¹ However, it carries the

risk of central nervous system (CNS) effects, including extrapyramidal symptoms such as dystonia and dyskinesia,^{12–14} and therefore has an FDA black box warning regarding chronic or high-dose treatment.¹¹ Domperidone, another dopamine D₂ receptor antagonist, provides similar symptom improvement to metoclopramide in gastroparesis, but is peripherally acting only, and therefore does not carry the same potential for CNS effects.¹⁵ Although approved by the European Medicines Agency for the short-term treatment of nausea and vomiting of variable origin,¹⁶ domperidone has not received FDA approval owing to associated cardiovascular risks, including cardiac arrhythmia, sudden cardiac death, and prolonged corrected QT (QTc) interval,^{17,18} which are most likely related to human ether-à-go-go-related gene (hERG) potassium channel inhibition.^{19–21}

Trazpiroben (previously referred to as TAK-906 or ATC-1906M) is a novel, peripherally selective dopamine D₂/D₃ receptor antagonist currently under development for the treatment of gastroparesis. Trazpiroben has been designed to retain the dopamine receptor antagonist profile and minimal CNS penetration of domperidone, without the associated cardiac effects. Owing to its peripheral selectivity, trazpiroben may be less likely to produce CNS effects; no CNS safety

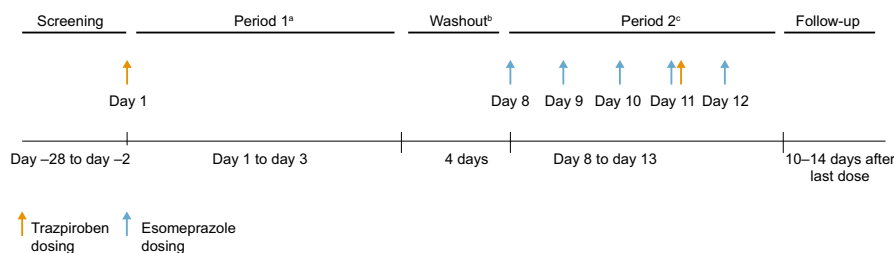


FIGURE 1 Study design. CRU, clinical research unit. ^aParticipants were confined at the CRU from day -1 of period 1 and released from the CRU after day 3 study assessments were completed. ^bA washout of at least 4 days between trazpiroben dosing in period 1 and first dosing in period 2. ^cParticipants returned to the CRU on the morning of days 8 and 9 of period 2 for dosing and/or study procedures as appropriate. Participants were confined to the CRU from the morning of day 10 until after the 48-h blood sampling on day 13

concerns have been identified during phase I or phase IIa of clinical development, and trazpiroben has shown low affinity for the hERG potassium channel, with no indication of effects on the QTc interval or electrocardiogram (ECG) measurements.²²⁻²⁴ Trazpiroben is primarily metabolized by a non-cytochrome P450 (CYP) pathway by multiple cytosolic nicotinamide adenine dinucleotide phosphate-dependent reductases (with minor contributions through CYP3A4 and CYP2C8), and is expected to have low potential for metabolic and transporter-mediated drug-drug interactions (DDIs) based on in vitro evaluations.²⁵ In clinical trials, single and multiple doses of trazpiroben have been shown to have a favorable safety profile, and the therapy was well-tolerated.^{24,26} To further evaluate the safety and tolerability of trazpiroben, a phase IIa study has also been conducted (NCT03268941), whereas a phase IIb study is currently ongoing (NCT03544229); both are in patients with idiopathic or diabetic gastroparesis.

In addition to gastroparesis, many affected patients may have comorbidities, including gastroesophageal reflux disease, anxiety, irritable bowel syndrome, and fibromyalgia,²⁷ for which they may receive several treatments concurrently. Accordingly, there is a need to understand the potential for DDIs between different therapies to ensure appropriate treatment dosing and reduce the risk of any resulting adverse events (AEs). Proton pump inhibitors (PPIs) are often used by patients with gastroparesis to manage gastroesophageal reflux symptoms.²⁸ As PPIs suppress gastric acid secretion by specific inhibition of the H⁺/K⁺-adenosine triphosphatase (ATPase) pump in gastric parietal cells,²⁹ these agents act to increase gastric pH for a sustained period of time, and may therefore alter the bioavailability of drugs with pH-dependent solubility when used together. The solubility of trazpiroben is pH-dependent and decreases with increasing pH, with prior testing demonstrating that trazpiroben has a mean solubility of 1.21 mg/ml at pH 1.15, compared with a solubility of 0.05 mg/ml at pH 6.97 (data on file). Based on its pH-dependent solubility, it was decided to evaluate the

potential for DDIs between trazpiroben and the PPI esomeprazole in a clinical study.^{30,31}

The aims of this study were to evaluate the effect of the PPI esomeprazole on the single-dose pharmacokinetics (PK) of oral trazpiroben, and to determine the safety and tolerability of a single oral dose of trazpiroben in the presence and absence of esomeprazole.

METHODS

Study design

This was a single-sequence, open-label, two-period, crossover study in healthy adults conducted between February 27, 2019, and April 15, 2019 (NCT03849690; [Figure 1](#)). The study included a screening visit conducted 28 days prior to dosing, followed by period 1 (days 1–3). Participants received a single oral dose of trazpiroben 25 mg after an overnight fast of at least 10 h on day 1 and continued to fast for at least 4 h postdose. Participants were confined in the clinical research unit (CRU) from day -1 to day 3, until after the 48-h post-trazpiroben dose blood sample had been taken.

Esomeprazole was selected for use in this study as it is currently one of the most prescribed PPIs, has a favorable safety profile, and its potential for DDIs has been extensively studied.^{29,32,33} Additionally, it is not expected to directly interact with trazpiroben, such as via the CYP3A4 enzyme.³⁴ Following a 4-day washout period after trazpiroben dosing in period 1, participants entered period 2 (days 8–13). During this study period, participants received esomeprazole 40 mg once daily on days 8–12. On days 8–10 and day 12, participants fasted for greater than or equal to 1 h pre and postdose relative to administration of esomeprazole. On day 11, participants were given a single oral dose of trazpiroben 25 mg 1 h after esomeprazole dosing, following an overnight fast for greater than or equal to 10 h prior to administration. Administration of esomeprazole 40 mg once daily for 3 days is considered

sufficient to reach steady-state inhibition of acid secretion.^{29,32} During period 2, study participants attended the CRU on days 8 and 9 for study dosing and/or assessments and were then confined in the CRU from the morning of day 10 until after the 48-h post-trazpiroben dose blood sample had been taken on day 13. The study ended with a follow-up period of 10–14 days after the last dose of trazpiroben.

All pertinent study documents were reviewed by the Advarra Institutional Review Board (IRB) prior to study initiation. The study protocol was reviewed and approved by the local IRB of the study site, and written informed consent was obtained from each participant in the study prior to enrollment. The study was conducted in compliance with the principles expressed in the Declaration of Helsinki and Good Clinical Practice regulations and guidelines.

Participants

Eligible participants were healthy men and women, continuous non-smokers, aged 18–55 years inclusive, with a body mass index (BMI) of greater than or equal to 18.0 and less than 30.0 kg/m². Participants were excluded if they were unable to refrain from, or anticipated the use of, any medication, herbal remedies, or vitamin supplements within 14 days prior to first dosing and throughout the study, or any substance known to significantly affect the disposition of study drugs within 28 days prior to the first dosing and for the study duration (please see further details in Table S1).

Pharmacokinetic analysis

Blood samples (4 ml) for determination of plasma concentrations of trazpiroben were collected on day 1 (period 1) and day 11 (period 2), predose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 h postdose (times relative to trazpiroben dosing). The 16-h postdose sampling was either on day 1 or day 2 in period 1, and day 11 or day 12 in period 2, depending on the respective time of the preceding trazpiroben dose. Plasma concentrations of trazpiroben were measured using a validated liquid chromatography/tandem mass spectrometry assay at Q2 Solutions (Ithaca, NY).³⁵ The analytical range of the assay was 0.05–50.00 ng/ml. PK parameters, including area under the curve (AUC) from time 0 extrapolated to infinity (AUC_∞), maximum serum concentration (C_{max}), time to C_{max} (T_{max}), and apparent first-order terminal elimination half-life (t_{1/2}), were calculated using a noncompartmental approach.

Safety and tolerability

The safety of trazpiroben was assessed by monitoring treatment-emergent adverse events (TEAEs), vital signs, and ECG (12-lead safety) parameters throughout the study and follow-up period. TEAEs were continuously monitored and assessed from day –1 until the follow-up visit 10–14 days after the final dose of trazpiroben. Vital signs and ECG parameters were assessed at screening, predose, and at 1, 2, 4, 8, and 48 h postdose (relative to trazpiroben) on days 1 and 3 of period 1, and days 11 and 13 of period 2, as well as at follow-up. Assessments were also performed on the final day of the study (day 13 of period 2), or prior to early withdrawal from the study.

Statistical methods

The sample size of this study was estimated to provide at least 80% power to conclude that the C_{max} of trazpiroben would not decrease by more than 50% in the presence of esomeprazole, assuming that the intra-subject coefficient of variation (CV%) for trazpiroben C_{max} would not exceed 45% and a true ratio of 0.8.

PK parameters were calculated from trazpiroben plasma concentration–time data for all evaluable participants using a standard noncompartmental analysis using Phoenix[®] WinNonlin[®] version 7.0 (Certara, Princeton, NJ), and summarized by treatment with descriptive statistics. Results below the limit of quantification were replaced with zero for the purposes of PK calculations. All concentration data were included in the calculation of the PK parameters, the individual concentration–time plots (based on actual sample times), and in the mean concentration–time plots (based on nominal sample times).

To evaluate the potential effect of esomeprazole on the PK of trazpiroben, an analysis of variance (ANOVA) was performed on the natural log-transformed trazpiroben AUC_∞ and C_{max} parameters, and the results were exponentiated to provide estimates on the original scale. The ANOVA model included treatment as a fixed effect and participant as a random effect; each ANOVA included calculation of least-squares means (LSMs) for these PK parameters, as well as the difference between treatment LSMs. The geometric mean ratios (GMRs; trazpiroben with esomeprazole relative to trazpiroben alone) and the associated 90% confidence intervals (CIs) were determined by exponentiation of the appropriate estimates for the difference between treatments in the natural log-transformed parameters.

TEAEs and continuous variables for vital signs and ECG parameters were summarized using sample size (*n*), mean, SD, and minimum, median, and maximum values, with measures calculated by treatment and time

point of measurement for vital signs and ECG parameters. Frequency counts and percentages were reported for categorical data when appropriate.

RESULTS

Participant disposition and baseline demographics

In total, 12 participants were included in the analysis, with all participants completing the study. Participants were predominantly men (67%), with a mean (SD) age and BMI of 37.8 (9.7) years and 25.3 (2.5) kg/m², respectively (Table 1).

Pharmacokinetic analysis

Plasma concentrations

Following a single dose of trazpiroben alone, or a single dose of trazpiroben in the presence of esomeprazole, the mean plasma concentration of trazpiroben peaked at around 1 h postdose and followed a biphasic decline with an approximate half-life of 6–7 h (Figure 2). Plasma concentrations of trazpiroben were quantifiable 1–12 h postdose in all participants following both administration of trazpiroben alone

and co-administration with esomeprazole. At 24 h postdose, plasma trazpiroben concentrations were below the limit of quantification in 50% of individuals following administration of trazpiroben alone, and in greater than 50% of participants following co-administration with esomeprazole.

Plasma PK parameters

Following the co-administration of trazpiroben with esomeprazole, the AUC_∞ and C_{max} of trazpiroben were comparable with the respective values following administration of trazpiroben alone, whereas similar median T_{max} values were observed following both treatments (Table 2). Elimination of trazpiroben, as assessed by the mean t_{1/2}, was similar following the co-administration of trazpiroben with esomeprazole versus administration of trazpiroben only. The geometric CV% for AUC_∞ and C_{max} were slightly higher following administration of trazpiroben with esomeprazole than following trazpiroben alone. Plasma trazpiroben AUC_∞ and C_{max} values, following administration of trazpiroben alone and in conjunction with esomeprazole, are presented in the box plots shown in Figure 3. The GMRs for plasma AUC_∞ and C_{max} were 11.8% and 12.8% lower following co-administration of trazpiroben and esomeprazole versus trazpiroben alone, respectively (Table 3).

TABLE 1 Summary of baseline participant demographics

Characteristic	Overall (N = 12)
Sex, n (%)	
Female	4 (33)
Male	8 (67)
Race, n (%)	
Asian	1 (8)
Black or African American	3 (25)
White	8 (67)
Ethnicity, n (%)	
Hispanic or Latino	8 (67)
Not Hispanic or Latino	4 (33)
Age, years	
Mean (SD)	37.8 (9.7)
Median	41.0
Minimum, maximum	23.0, 54.0
BMI, kg/m ²	
Mean (SD)	25.3 (2.5)
Median	25.2
Minimum, maximum	21.8, 29.4

Abbreviation: BMI, body mass index.

Safety analysis

All 12 participants were included in the safety analysis. No deaths, serious AEs, or discontinuations due to AEs were reported in this study. In total, eight AEs were reported by six participants (50%), including two participants receiving trazpiroben alone (headache and throat irritation), one individual receiving esomeprazole alone (oropharyngeal pain), and three participants following co-administration of esomeprazole and trazpiroben (influenza-like illness, vessel puncture site reaction and pain, folliculitis, and delayed menstruation; Table 4). Except for one AE (an event of influenza-like illness following the co-administration of esomeprazole and trazpiroben, deemed moderate in severity), all AEs were considered mild in severity. Overall, most (6/8; 75%) AEs were considered unrelated to either study treatment. One AE was considered related to trazpiroben administered alone (headache, mild severity) and another AE (delayed menstruation, mild severity) related to both trazpiroben and esomeprazole.

There were no treatment-related trends noted in vital signs, ECG, or laboratory data in this study. Mean vital sign and ECG results remained within normal limits following both treatments, and no clinically meaningful changes in these parameters were observed. Likewise, there were no

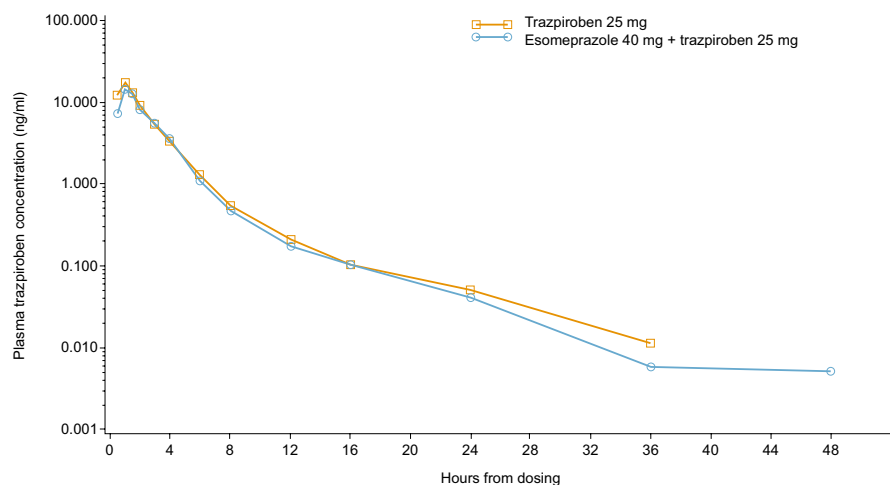


FIGURE 2 Arithmetic mean plasma trazpiroben concentration versus time profiles following a single oral dose of trazpiroben 25 mg alone and multiple oral doses of esomeprazole 40 mg with a single oral dose of trazpiroben 25 mg

Parameter	Trazpiroben 25 mg (N = 12)	Trazpiroben 25 mg and esomeprazole 40 mg (N = 12)
AUC _∞ , ng h/ml		
Geo. mean (CV%)	44.03 (27.50)	38.85 (31.10)
C _{max} , ng/ml		
Geo. mean (CV%)	19.76 (36.50)	17.24 (40.50)
T _{max} , h		
Median (min, max)	1.00 (0.50, 1.53)	1.00 (0.50, 3.00)
t _{1/2} , h		
Mean (±SD)	6.21 ± 3.96	7.48 ± 9.10
CL/F, L/h		
Geo. mean (CV%)	567.90 (27.50)	643.50 (31.10)
V _z /F, L		
Geo. mean (CV%)	4137.00 (77.80)	4716.00 (102.00)

TABLE 2 Plasma PK parameters of trazpiroben in healthy participants

Note: No sample was collected at 36 h postdose for one individual following a single oral dose of trazpiroben 25 mg alone owing to difficult venipuncture.

Abbreviations: AUC_∞, area under the concentration–time curve from time 0 extrapolated to infinity; CL/F, apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration; C_{max}, maximum observed concentration; CV%, percentage coefficient of variation; Geo., geometric; PK, pharmacokinetic; t_{1/2}, apparent first-order terminal elimination half-life; T_{max}, time to reach maximum observed concentration; V_z/F, apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration.

clinically relevant shifts in laboratory values during the study and no individual out-of-range laboratory values were considered clinically relevant.

DISCUSSION

Gastroparesis is associated with significant patient burden, yet long-term use of current treatment options remains limited by the risk of serious side effects or the lack of regulatory approval. Given that patients with gastroparesis may

often be receiving multiple medications for symptomatic management or comorbidities, the potential for DDIs must be considered for any therapy under development.²⁷ In this study, we assessed the implications of PPI use on the pH-dependent solubility of trazpiroben in healthy participants, by evaluating the single-dose PK, safety, and tolerability of oral trazpiroben alone and when administered in conjunction with the PPI esomeprazole, which inhibits gastric acid secretion by suppressing H⁺ formation through inhibition of the H⁺/K⁺ ATPase enzyme system at the secretory surface of gastric parietal cells.³⁶

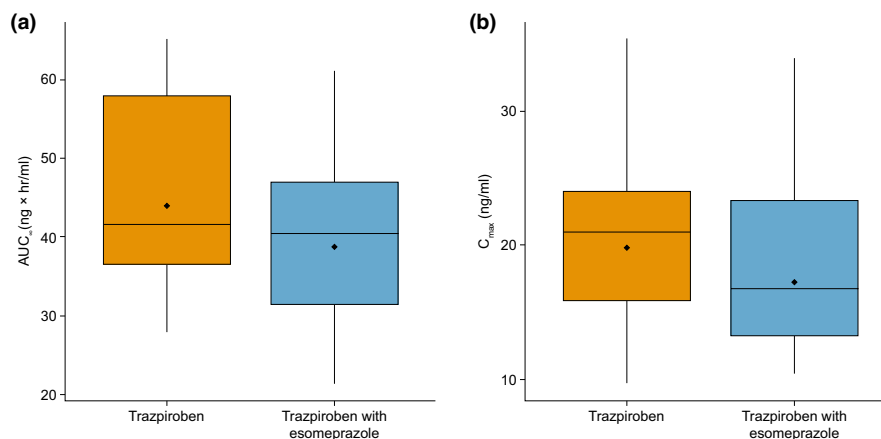


FIGURE 3 Box plots for the comparison of individual plasma trazpiroben AUC_{∞} (a) and C_{max} (b) for healthy participants receiving trazpiroben alone, and in the presence of esomeprazole. The lower and upper hinges correspond to the 25th and 75th percentiles, and the upper/lower whiskers extend from the hinge to no further than 1.5 times the interquartile range. The horizontal line inside the box represents the median, and the diamond symbol indicates the geometric mean value. AUC_{∞} , area under the concentration–time curve from time 0 extrapolated to infinity; C_{max} , maximum observed concentration

TABLE 3 Summary of statistical comparisons of plasma trazpiroben pharmacokinetic parameters

Parameter	Trazpiroben 25 mg (N = 12)	Trazpiroben 25 mg and esomeprazole 40 mg (N = 12)	GMR (90% CI)	Intra-participant CV%
	Geometric LSM	Geometric LSM		
AUC_{∞} , ng h/ml	44.03	38.85	0.882 (0.78–1.00)	16.74
C_{max} , ng/ml	19.76	17.24	0.872 (0.70–1.09)	31.57

Abbreviations: AUC_{∞} , area under the concentration–time curve from time 0 extrapolated to infinity; CI, confidence interval; C_{max} , maximum observed concentration; CV%, percentage coefficient of variation; GMR, geometric mean ratio; LSM, least-squares mean.

PK analyses showed that the AUC_{∞} and C_{max} of trazpiroben when co-administered with esomeprazole were similar to the values following trazpiroben treatment alone, indicating no clinically meaningful differences related to co-administration of esomeprazole. The present study was conducted following a preliminary framework for the assessment of pH-dependent DDIs for weak base drugs based on solubility data.³¹ Following completion of the current study, subsequent guidance from the FDA in 2020 provided a decision framework to evaluate the need for clinical DDI studies with acid-reducing agents.³⁰ The solubility profile of trazpiroben supports the need for a clinical examination of DDIs under this guidance, although a clinically meaningful DDI was not detected in this study. Multiple doses of once-daily esomeprazole 40 mg produces a steady-state inhibition of acid secretion,^{29,32} which is considered a worst-case scenario for evaluating near maximal gastric pH elevation.³¹ It is not expected that other acid-reducing agents, such as antacids and H_2 receptor antagonists, would affect trazpiroben PK by gastric pH-dependent interaction to a greater extent than is reported in this study.³⁷

As other PPIs may be selected to manage gastric acid-related disorders, the potential for interactions with these medications as a wider class should be considered.³⁸ Omeprazole carries the potential for drug interactions owing to its high affinity for the CYP2C19 enzyme, its moderate affinity for CYP3A4, and inhibition of both of these enzymes,³⁹ whereas lansoprazole, pantoprazole, and rabeprazole appear to have weaker potential for interactions than omeprazole.^{38,40,41} With regard to other acid-reducing agents, histamine H_2 receptor antagonists may have the potential for CYP-mediated interactions, primarily through CYP1A2, CYP2D6, and CYP3A4/5, although clinically meaningful effects of these interactions are limited.^{37,42} However, trazpiroben is primarily metabolized via cytosol reductase, with only minor levels of metabolism occurring via the CYP3A4 and CYP2C8 enzymes,²⁵ suggesting that other PPIs, histamine H_2 receptor antagonists, or antacids may be unlikely to affect the PK properties of trazpiroben through CYP-mediated DDIs.

Trazpiroben appeared well-tolerated and no safety signals for trazpiroben were observed following administration to healthy participants, either as a single agent or when co-administered with esomeprazole. No deaths,

TABLE 4 Overview of AEs in healthy participants

Participants reporting AEs, n (%)	Trazpiroben 25 mg ^a	Esomeprazole 40 mg ^b	Esomeprazole 40 mg + trazpiroben 25 mg ^c	Multiple doses of esomeprazole 40 mg + single dose of trazpiroben 25 mg ^d	Overall
Number of participants with treatment-emergent AEs	2 (17)	1 (8)	3 (25)	4 (33)	6 (50)
General disorders and administration site conditions	0 (0)	0 (0)	2 (17)	2 (17)	2 (17)
Influenza-like illness	0 (0)	0 (0)	1 (8)	1 (8)	1 (8)
Vessel puncture site pain	0 (0)	0 (0)	1 (8)	1 (8)	1 (8)
Vessel puncture site reaction	0 (0)	0 (0)	1 (8)	1 (8)	1 (8)
Infections and infestations	0 (0)	0 (0)	1 (8)	1 (8)	1 (8)
Folliculitis	0 (0)	0 (0)	1 (8)	1 (8)	1 (8)
Nervous system disorders	1 (8)	0 (0)	0 (0)	0 (0)	1 (8)
Headache	1 (8)	0 (0)	0 (0)	0 (0)	1 (8)
Reproductive system and breast disorders	0 (0)	0 (0)	1 (8)	1 (8)	1 (8)
Menstruation delayed	0 (0)	0 (0)	1 (8)	1 (8)	1 (8)
Respiratory, thoracic, and mediastinal disorders	1 (8)	1 (8)	0 (0)	1 (8)	2 (17)
Oropharyngeal pain	0 (0)	1 (8)	0 (0)	1 (8)	1 (8)
Throat irritation	1 (8)	0 (0)	0 (0)	0 (0)	1 (8)

Note: If a participant had two or more clinical adverse events, they were counted only once within a category. The same participant may appear in different categories.

Abbreviation: AE, adverse event.

^aSingle oral dose of trazpiroben 25 mg administered alone on day 1.

^bEsomeprazole alone (from first esomeprazole dosing and prior to trazpiroben dosing).

^cEsomeprazole + trazpiroben (following trazpiroben dosing on day 11 of period 2).

^dMultiple oral doses of esomeprazole 40 mg administered once daily on days 8–12 with a single oral dose of trazpiroben 25 mg administered on day 11.

serious AEs, or discontinuations occurred, and seven of the eight AEs reported were mild in severity. Notably, no CNS or cardiovascular safety concerns were observed in this study, building on previous observations from prior preclinical and clinical studies, including trials conducted in US and Japanese participants.^{24,26}

Limitations of this study must be considered. This DDI study was conducted in a small number of healthy volunteers, and has a shorter study duration than an actual clinical regimen scenario; however, similar drug interaction observations are expected in patients with gastroparesis based on the known characteristics of trazpiroben.

CONCLUSION

In healthy adults, no clinically meaningful DDI was observed for trazpiroben following co-administration of the PPI esomeprazole compared with administration of trazpiroben alone, and both treatments were well-tolerated. Exposure to trazpiroben, as assessed by AUC_{∞} and C_{max} , was shown to be similar when trazpiroben was co-administered with esomeprazole compared to trazpiroben administration alone. The lack of any clinically meaningful DDI suggests that esomeprazole may be co-administered with trazpiroben.

ACKNOWLEDGEMENTS

Medical writing assistance was provided by Luke Bratton and Alexandra Kisbey-Ascott of Oxford PharmaGenesis, Oxford, UK and was supported by Takeda Development Center Americas, Inc.

CONFLICT OF INTEREST

Jatinder K. Mukker was formerly an employee of Takeda Development Center Americas, Inc. and received stock or stock options. She is currently an employee of EMD Serono Research & Development Institute, Inc. George Dukes was an employee of Takeda Development Center Americas, Inc. and received stock or stock options at the time of the study. He is currently an employee of Ironwood Pharmaceuticals, Inc. Lisi Wang, Susanna Huh, and Polyna Khudyakov are employees of Takeda Development Center Americas, Inc. and receive stock or stock options. Mitsuhiro Nishihara is an employee of Takeda Pharmaceutical Company, Ltd. Chunlin Chen was an employee of Takeda Development Center Americas, Inc. and received stock or stock options at the time of the study. He is currently an employee of Bayer Pharmaceuticals.

AUTHOR CONTRIBUTIONS

J.K.M., G.D., L.W., S.H., P.K., M.N., and C.C. wrote the manuscript. G.D., M.N., and C.C. designed the research.

C.C. performed the research. J.K.M., G.D., L.W., S.H., P.K., and M.N. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Mukker JK, Dukes G, Wang L, et al. Evaluation of the pharmacokinetics of trazpiroben (TAK-906) in the presence and absence of the proton pump inhibitor esomeprazole. *Clin Transl Sci.* 2022;15:1281-1290. doi:[10.1111/cts.13248](https://doi.org/10.1111/cts.13248)