Effect and safety of anaprazole in the treatment of duodenal ulcers: a randomized, rabeprazole-controlled, phase III non-inferiority study

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Abstract

Background: The pharmacokinetic and clinical behaviors of many proton pump inhibitors (PPIs) in peptic ulcer treatment are altered by *CYP2C19* genetic polymorphisms. This non-inferiority study evaluated the efficacy and safety of the novel PPI anaprazole compared with rabeprazole. We also explored the influence of *Helicobacter pylori* (*H. pylori*) infection status and *CYP2C19* polymorphism on anaprazole.

Methods: In this multicenter, randomized, double-blind, double-dummy, positive-drug parallel-controlled, phase III study, Chinese patients with duodenal ulcers were randomized 1:1 to receive rabeprazole 10 mg + anaprazole placebo or rabeprazole placebo + anaprazole 20 mg once daily for 4 weeks. The primary efficacy endpoint was the 4-week ulcer healing rate assessed by blinded independent review. Secondary endpoints were the proportion of patients with improved overall and individual duodenal ulcer symptoms at 4 weeks. Furthermore, exploratory subgroup analysis of the primary endpoint by *H. pylori* status and *CYP2C19* polymorphism was conducted. Adverse events were monitored for safety. Non-inferiority analysis was conducted for the primary endpoint.

Results: The study enrolled 448 patients (anaprazole, $n = 225$; rabeprazole, $n = 223$). The 4-week healing rates were 90.9% and 93.7% for anaprazole and rabeprazole, respectively (difference, −2.8% [95% confidence interval, −7.7%, 2.2%]), demonstrating non-inferiority of anaprazole to rabeprazole. Overall duodenal ulcer symptoms improved in 90.9% and 92.5% of patients, respectively. Improvement rates of individual symptoms were similar between the groups. Healing rates did not significantly differ by *H. pylori* status or *CYP2C19* genotype for either treatment group. The incidence of treatment-emergent adverse events was similar for anaprazole (72/220, 32.7%) and rabeprazole (84/219, 38.4%).

Conclusions: The efficacy of anaprazole is non-inferior to that of rabeprazole in Chinese patients with duodenal ulcers.

Registration: ClinicalTrials.gov, NCT04215653.

Keywords: Cytochrome P-450 *CYP2C19*; Non-inferiority trial; Peptic ulcer; Polymorphism; Genetic; Proton pump inhibitors; Anaprazole; Rabeprazole

Introduction

In peptic ulcer disease, excessive gastric acid or pepsin secretion causes the gastrointestinal mucosa to become inflamed and the tissue to become necrotic, leading to ulcer formation.[1] Peptic ulcer incidence rates vary by country and few data are available to determine these rates. A study published in 2010 reported an incidence rate of 17.2% among residents of Shanghai, which is much higher compared with the 4.1% incidence reported for

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Western populations.[2] Patients with peptic ulcer disease often experience epigastric pain associated with dyspepsia, bloating, abdominal fullness, or early satiety. Most cases are caused by *Helicobacter pylori* (*H. pylori*) infection or non-steroidal anti-inflammatory drug use.[3]

Proton pump inhibitors (PPIs) are a mainstay of peptic ulcer treatment that act by irreversibly inhibiting H^+/K^+-ATPase. Both conventional PPIs and potassium-competitive acid blockers are available.[4,5] While effective, these treatment modalities can be improved. Nearly 40% of patients taking PPIs twice daily increase their dose because of persistent nocturnal symptoms.[6] Furthermore, PPIs undergo extensive cytochrome *CYP2C19*-catalyzed hepatic biotransformation.[7,8] The pharmacokinetic and clinical behaviors of many PPIs are altered by *CYP2C19* genetic polymorphisms, especially in Asian patients.[9] The proportion of patients with the poor *CYP2C19* metabolizer phenotype is much lower in Caucasians (2–6%) than Asians (Japanese, 19–23%; Chinese, 15%; Korean, 13%).[10]

Anaprazole is a novel PPI in development for peptic ulcer treatment. PPIs are substituted 2-pyridyl methylsulfinyl benzimidazoles that share a similar core structure. However, in anaprazole, the benzimidazole has been added as a furan ring. In an *in vitro* study, approximately 50% of anaprazole was metabolized via a thioether non-enzymatic reduction mechanism.[11] The remaining anaprazole was metabolized in the liver by P450 cytochromes including 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4. In total, the contribution of 2C19 was only 3.5%. Preclinical and phase I studies have shown that anaprazole has an equivalent half-life and pharmacodynamic profile, and an improved safety profile, compared with rabeprazole.[11,12] Patients treated with 10 mg or 20 mg rabeprazole experience high rates of ulcer healing and clinical symptom relief.[13,14] A phase II study reported similar duodenal ulcer healing rates of anaprazole and rabeprazole treatments.[11] Although these results are encouraging, a comparison of the efficacy and safety of anaprazole with rabeprazole in a larger patient population is needed. This phase III study was conducted to confirm non-inferior efficacy of anaprazole to rabeprazole in the treatment of Chinese patients with duodenal ulcers. Safety was also evaluated and two subgroup analyses were conducted to investigate the effect of *H. pylori* infection and *CYP2C19* polymorphisms on the clinical efficacy of anaprazole.

Methods

Patients

Patients admitted to 41 study centers [Supplementary Table 1, http://links.lww.com/CM9/B356] in China from January 18, 2020 to December 9, 2020, aged 18 to 70 years, diagnosed by gastroscopy with a stage A1 or A2 duodenal ulcer within 7 days prior to randomization, and with 1 to 2 ulcers (3–15 mm diameter) were included. Major exclusion criteria were the presence of cancerous ulcers, compound and stress ulcers, esophageal erosion, reflux esophagitis, or Zollinger–Ellinger syndrome; severe complications, such as pyloric obstruction, hemorrhage (Forrest type I, IIa, and IIb), and perforation; a current gastric ulcer; a history of inflammatory bowel disease; esophageal or gastric varices; use of PPIs within 5 days before randomization or for >3 consecutive days within 28 days before randomization; treatment with triple or quadruple anti-*H. pylori* therapy within 28 days of randomization; use of drugs that can cause ulcers or bleeding ulcers (e.g., systemic glucocorticoid therapy, non-steroidal anti-inflammatory drug, and anticoagulants) for >3 consecutive days within 28 days of randomization; elevated liver enzymes (>1.5 × upper limit of normal); and elevated levels (>upper limit of normal) of thyroid-stimulating hormone, serum free triiodothyronine, or serum free thyroxine. All patients had provided written informed consent.

Study design and ethical approval

This study was conducted in accordance with the ethical principles of the *Declaration of Helsinki* and the ethical requirements of the Chinese Drug Clinical Trial Quality Management Code. The protocol was approved by the Shanghai Changhai Hospital Ethics Committee (CHEC2019-176) and the study was registered at ClinicalTrials.gov (NCT04215653).

This multicenter, randomized, double-blind, double-dummy, positive-drug parallel-controlled, phase III, non-inferiority study compared the efficacy and safety of anaprazole with rabeprazole in Chinese patients with duodenal ulcers. Following the screening period and enrollment by study investigators, patients were randomized 1:1 to receive 10 mg rabeprazole + anaprazole placebo or rabeprazole placebo + 20 mg anaprazole once daily (oral) before breakfast for 4 weeks. Ulcer staging was performed by blinded independent central review (BICR) and endoscopic staging of duodenal ulcers was performed in accordance with the People's Republic of China Health Industry Standard (WS317–2010) diagnostic criteria (A: active stage; H: healing stage; S: scar stage). The *H. pylori* infection status was determined by the C13 urea breath test.[15] Patients did not receive antibiotics during the study. Fluorescence polymerase chain reaction and Sanger sequencing were used to detect *CYP2C19* polymorphisms. *H. pylori*-positive patients were treated with bactericidal therapy in accordance with their informed preference after the study.

The study duration was approximately 9 weeks with a screening period (day −21 to −1), a 4-week treatment period, and a 2-week safety follow-up period. Patients had one study visit during the screening period, one at baseline, two during the treatment period (2 weeks and end of treatment [4 weeks or early withdrawal]), and one at the safety follow-up (2 weeks after the final treatment of the study drug). Blood and urine were collected at the screening visit and both visits during the treatment period. Safety evaluations were conducted at all visits.

A randomization scheme stratified by baseline *H. pylori* status (positive or negative) and history of peptic ulcers (with or without) was used (1:1 assignment). Randomization scheme was generated by independent, unblinded statistician. Randomization was performed using the

Interactive Web Response System (IWRS, Omega CRO, Ankara, Turkey).

A double-blind design was adopted and unblinding was allowed for an emergency, serious adverse event (SAE), and at the request of the study investigator. Concomitant use of antacids containing magnesium hydroxide or aluminum hydroxide was allowed. Histamine H2 receptor antagonists and drugs that may interact with PPIs were not allowed. Treatment compliance was monitored by a daily diary card that was checked by the study investigator.

Outcomes

The primary efficacy endpoint was the ulcer healing rate at week 4 assessed using endoscopy images and judged by BICR. Secondary efficacy endpoints included the proportion of patients with improved severity of duodenal ulcer symptoms both overall and individual (abdominal pain, bloating, burning sensation, acid reflux, nausea, vomiting, and belching). Exploratory endpoints included the number of days to resolution of duodenal ulcer abdominal pain and nocturnal abdominal pain. Subgroup analyses were conducted to determine the primary efficacy endpoint by *H. pylori* infection status and *CYP2C19* polymorphism (rapid metabolizer [RM], intermediate metabolizer [IM], and poor metabolizer [PM]).

Adverse events (AEs), vital signs, physical and laboratory examinations, and electrocardiograms were assessed for safety. AEs were coded in accordance with the system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities, version 23.1. AEs were graded in accordance with the Common Terminology Criteria for Adverse Events, version 5.0. Safety follow-up was conducted through telephone visits.

Statistical methods

A sample size of 448 patients was estimated based on the non-inferiority assumption of a duodenal ulcer healing rate of 88% at week 4 of treatment,[11] a 10% non-inferiority margin, and a 15% dropout rate. This would provide 85% power to compare efficacy between anaprazole and rabeprazole at a significance level of 2.5% (one-sided). Primary and secondary endpoint analyses were based on the full analysis set (FAS) and per-protocol analysis set (PPS). Exploratory endpoints analyses were based on the FAS. Safety analyses were based on the safety set (SS) (described in Supplementary Text 1, http://links.lww.com/CM9/B356).

Continuous variables were summarized with mean and standard deviation. Categorical variables were summarized with number of cases and percentage (%). Missing efficacy values were imputed using the last observation carried forward method. Primary endpoint was analyzed based on non-inferiority testing. The difference in healing rate and its 95% confidence interval (CI) in the anaprazole group relative to the rabeprazole group at week 4 was calculated using Wald's asymptotic method. If the lower limit of the 95% CI was greater than −10% (non-inferiority margin), anaprazole was considered non-inferior to rabeprazole. For the secondary endpoint, the difference in both overall and individual symptoms and its 95% CI in the anaprazole group relative to the rabeprazole group at week 4 was calculated using Wald's asymptotic method and Newcombe–Wilson method. For the exploratory endpoint, the median time to pain disappearance and its 95% CI were estimated by the Kaplan–Meier method. Subgroup analyses were conducted by *H. pylori* status (positive or negative) or *CYP2C19* genotype polymorphism (RM, IM, or PM). *P*-values were estimated using the chi-squared or Fisher's exact test, and a two-sided *P*-value <0.05 was considered statistically. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patients

This study was conducted between January 18, 2020 and December 9, 2020 at 41 study centers in China. Of the 551 patients screened, 448 were enrolled and randomized to treatment (anaprazole, $n = 225$; rabeprazole, $n = 223$) [Figure 1]. Overall, 432 patients (96.4%) completed the study (anaprazole, $n = 214$ [95.1%]; rabeprazole, $n = 218$ [97.8%]). The most common reason for discontinuation in both groups was patient withdrawal. There were 220 and 222 patients in the anaprazole and rabeprazole groups in the FAS, 210 and 208 in the PPS, and 220 and 219 in the SS, respectively. The study was carried to completion. A total of 0.2% (1/448) of patients were lost to follow-up.

A significantly higher proportion of patients in the anaprazole *vs.* rabeprazole group had stage A1 (i.e., clinically more severe) ulcers. There were no other statistically significant differences in patient demographics or baseline characteristics between the groups [Table 1]. In total, 81.7% of patients were positive for *H. pylori* and 21.5% had a recurring ulcer. Abdominal pain (74.2%, 328/442) and nocturnal abdominal pain (40.5%, 179/442) were the most common symptoms in all patients.

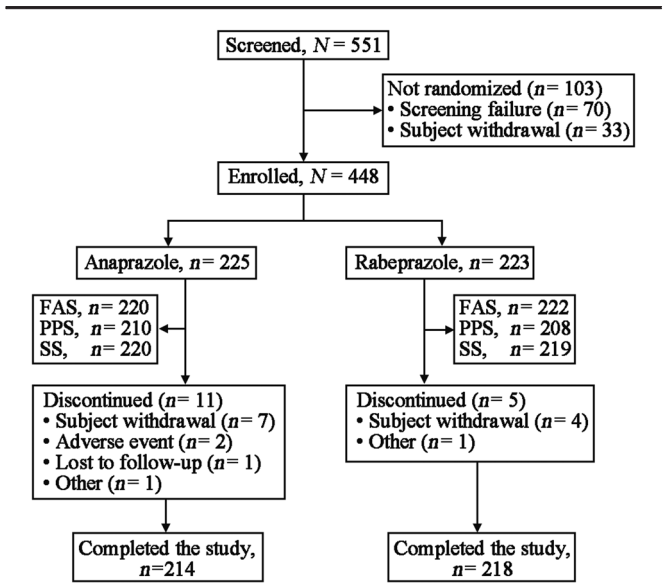

Figure 1: Patient disposition. FAS: Full analysis set; PPS: Per-protocol set; SS: Safety set.

Most patients took 80% to 120% of their study medication (anaprazole, 98.2% [216/220]; rabeprazole, 97.7% [217/222]) and 1.8% (4/220) and 2.3% (5/222) of patients in anaprazole and rabeprazole groups, respectively, took <80% of their study medication.

Efficacy outcomes

The 4-week healing rate by BICR (primary efficacy endpoint) in the FAS population was 90.9% with anaprazole and 93.7% with rabeprazole (healing rate difference: −2.8%; 95% CI: −7.7%, 2.2%) [Table 2]. In the PPS population, the rates were 93.3% and 96.6%, respectively (difference: −3.3%; 95% CI: −7.5%, 0.9%). For both populations, the lower limit of the 95% CI was greater than −10%, demonstrating non-inferiority of anaprazole to rabeprazole in both analysis sets. These findings were supported by the secondary analyses.

After 4 weeks of treatment, overall duodenal ulcer symptoms were improved in 90.9% (95% CI: 86.8%, 95.0%) and 92.5% (95% CI: 88.7%, 96.3%) of patients in the anaprazole and rabeprazole groups, respectively [Table 3]. Improvement rates were similar for abdominal pain (92.2% and 92.0%), bloating (81.9% and 89.8%), burning sensation (100% and 100%), acid reflux (93.8% and 97.1%), nausea (100% and 94.7%), and vomiting (100% and 100%). For belching, the response rates were somewhat lower with anaprazole than rabeprazole (75.7% *vs*. 92.1%).

Exploratory outcomes

Pain was eliminated by treatment in 96.4% (160/166) and 98.8% (160/162) of patients in anaprazole and rabeprazole groups, respectively, who had abdominal pain at baseline. The median (95% CI) time to elimination was 2 (2, 3) days and 2 (1, 2) days, respectively [Table 4]. Pain was eliminated by treatment in 96.6% (85/88) and 98.9% (90/91) of patients in the anaprazole and rabeprazole groups, respectively, who had baseline nocturnal abdominal pain. The median (95% CI) time to elimination was 2 (2, 3) days and 1 (1, 2) day, respectively.

Blood samples from 200 patients were collected for *CYP2C19* polymorphism determination during the screening period. The *CYP2C19* genotype was determined in 196 of these patients (anaprazole, $n = 104$; rabeprazole, $n = 92$). There were no statistically significant differences between groups in terms of demographic and clinical

Table 1: Demographic and clinical characteristics, and endoscopic findings in the FAS population with duodenal ulcer.

Parameters	Anaprazole ($n = 220$)	Rabeprazole ($n = 222$)	Total ($n = 442$)	Statistic value	P^*
Demographic and clinical characteristics					
Age (years)	40.9 ± 11.1	42.9 ± 11.5	41.9 ± 11.3	–1.89	0.06
Male	140 (63.6)	137 (61.7)	277 (62.7)	0.18	0.68
Height (cm)	166.4 ± 8.7	165.4 ± 7.7[†]	165.9 ± 8.2[‡]	1.28	0.20
Weight (kg)	63.4 ± 11.8	62.4 ± 10.7	62.9 ± 11.3	0.99	0.32
BMI (kg/m^2)	22.8 ± 3.1	22.7 ± 3.2[†]	22.8 ± 3.2[‡]	0.23	0.82
Peptic ulcer history	48 (21.8)	47 (21.2)	95 (21.5)	0.03	0.87
Helicobacter pylori positive	179 (81.4)	182 (82.0)	361 (81.7)	0.03	0.87
Endoscopic findings					
No. of ulcers					
1	181 (82.3)	188 (84.7)	369 (83.5)	0.68	0.50
2	39 (17.7)	34 (15.3)	73 (16.5)		
Maximum ulcer area (mm^2)	35.9 ± 25.2	33.9 ± 24.6	34.9 ± 24.9	0.86	0.39
Duodenal ulcer stage[§]					
A1	175 (79.5)	158 (71.2)	333 (75.3)	–2.04	0.04
A2	45 (20.5)	64 (28.8)	109 (24.7)		

Data are presented as *n* (%) or mean ± SD. Stage A1, the surface of the ulcer is necrotic, covered with thick white moss or showing a yellow white valley with obvious surrounding hyperemia and edema. Stage A2, the surface of the ulcer is necrotic, covered with thin white moss with obvious surrounding hyperemia and edema. [*] *P*-values were calculated using the *t*-test (continuous variables), chi-squared test (unordered categorical variables), or Wilcoxon rank-sum test (ordered categorical variables). [†] $N = 221$. [‡] $N = 441$. [§] Active stages A1 and A2 (People's Republic of China Health Industry Standard [WS317–2010]). BMI: Body mass index; FAS: Full analysis set; SD: Standard deviation.

Table 2: Healing rates of duodenal ulcers after 4 weeks of treatment for patients with duodenal ulcer.

Treatments	Healing rates	
	FAS (nA = 220, nR = 222)	PPS (nA = 210, nR = 208)
Anaprazole, % (95% CI)	90.9 (87.1, 94.7)	93.3 (90.0, 96.7)
Rabeprazole, % (95% CI)	93.7 (90.5, 96.9)	96.6 (94.2, 99.1)
Difference in healing rates, % (anaprazole–rabeprazole, 95% CI)	−2.8 (−7.7, 2.2)	–3.3 (–7.5, 0.9)

CI: Confidence interval; FAS: Full analysis set; PPS: Per-protocol analysis set; nA: Number of anaprazole group; nR: Number of rabeprazole group. 95% CIs were estimated by the Wald asymptotic method.

Table 3: Symptom improvement at 4 weeks among patients with duodenal ulcer.

Symptom	FAS			PPS		
	Anaprazole (n = 220)	Rabeprazole (n = 222)	Difference (ana–rab, 95% CI)	Anaprazole (n = 210)	Rabeprazole (n = 208)	Difference (ana–rab, 95% CI)
Overall symptoms						
No. of patients	187	186		177	175	
Improvement, % (95% CI)	90.9 (86.8, 95.0)	92.5 (88.7, 96.3)	−1.6 (−7.2, 4.0)	93.2 (89.5, 96.9)	94.3 (90.8, 97.7)	−1.1 (−6.1, 4.0)
Severity of abdominal pain						
No. of patients	166	162		158	152	
Improvement, % (95% CI)	92.2 (88.1, 96.3)	92.0 (87.8, 96.2)	0.2 (−5.7, 6.0)	94.3 (90.7, 97.9)	94.1 (90.3, 97.8)	0.2 (−5.0, 5.4)
Severity of bloating						
No. of patients	72	88		68	85	
Improvement, % (95% CI)	81.9 (73.1, 90.8)	89.8 (83.4, 96.1)	−7.8 (−18.3, 3.1)	85.3 (76.9, 93.7)	91.8 (85.9, 97.6)	−6.5 (−16.7, 3.8)
Severity of burning sensation						
No. of patients	19	24		18	24	
Improvement, % (95% CI)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	0 (−16.8, 13.8)*	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	0 (−17.6, 13.8)*
Severity of acid reflux						
No. of patients	32	34		31	33	
Improvement, % (95% CI)	93.8 (85.4, 100.0)	97.1 (91.4, 100.0)	−3.3 (−13.4, 6.8)	93.5 (84.9, 100.0)	97.0 (91.1, 100.0)	−3.4 (−13.9, 7.0)
Severity of nausea						
No. of patients	16	19		16	18	
Improvement, % (95% CI)	100.0 (100.0, 100.0)	94.7 (84.7, 100.0)	5.3 (−4.8, 15.3)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	0 (−19.4, 17.6)*
Severity of vomiting						
No. of patients	4	7		4	6	
Improvement, % (95% CI)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	0 (−49.0, 35.4)*	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	0 (−49.0, 39.0)*
Severity of belching						
No. of patients	37	38		34	37	
Improvement, % (95% CI)	75.7 (61.9, 89.5)	92.1 (83.5, 100.0)	−16.4 (−32.7, −0.2)	79.4 (65.8, 93.0)	91.9 (83.1, 100)	−12.5 (−28.7, 3.7)

Ana: Anaprazole; CI: Confidence interval, FAS: Full analysis set; PPS: Per-protocol set; Rab: Rabeprazole. * 95% CI were estimated by the Newcombe–Wilson method.

Table 4: Median time to duodenal ulcer abdominal and nocturnal abdominal pain disappearance (FAS).

Parameters	Anaprazole (n = 220)	Rabeprazole (n = 222)
Patients with abdominal pain symptoms at baseline (n [%])	166 (75.5)	162 (73.0)
Median time to abdominal pain disappearance (days [95% CI])	2.0 (2.0, 3.0)	2.0 (1.0, 2.0)
Patients with nocturnal abdominal pain symptoms at baseline (n [%])	88 (40.0)	91 (41.0)
Median time to nocturnal abdominal pain disappearance (days [95% CI])	2.0 (2.0, 3.0)	1.0 (1.0, 2.0)

CI: Confidence interval; FAS: Full analysis set. The median time to disappearance of abdominal pain and its 95% CI were estimated by the Kaplan–Meier method.

characteristics when analyzed by *CYP2C19* genotype. PM, IM, and RM genotypes were reported in 13.3%, 43.9%, and 42.9% of all patients, respectively. There were no statistically significant differences in healing rates when analyzed by *CYP2C19* genotype for either treatment group [Table 5]. Healing rates for *H. pylori*-negative and -positive patients were 85.4% and 92.2%, respectively, in the anaprazole group ($P = 0.29$) and 95.0% and 93.4% in the rabeprazole group ($P = 0.99$). At baseline, the maximum ulcer area in anaprazole group was unbalance between *H. pylori*-negative and positive groups.

Safety

A summary of AEs is shown in Table 6. There were three (1.4%) SAEs in the anaprazole group (herpes zoster, chest discomfort, and ureteral calculi), which were all judged to

Table 5: Healing rates in accordance with the *CYP2C19* genotype and *Helicobacter pylori* subgroup (FAS) among patients with duodenal ulcer.

Subgroups	Anaprazole		Rabeprazole	
	Total	Healing rate	Total	Healing rate
CYP2C19 subgroup	$n = 104$		$n = 92$	
RM	42 (40.3)	38 (90.5)	42 (45.7)	40 (95.2)
IM	46 (44.2)	43 (93.5)	40 (43.5)	35 (87.5)
PM	16 (15.4)	16 (100)	10 (10.9)	10 (100)
P value	0.59		0.36	
H. pylori subgroup	$n = 220$		$n = 222$	
H. pylori positive	179 (81.4)	165 (92.2)	182 (82.0)	170 (93.4)
H. pylori negative	41 (18.6)	35 (85.4)	40 (18.0)	38 (95.0)
Chi-squared statistic	1.14		0	
P value	0.29		0.99	

Data are presented as *n* (%). FAS: Full analysis set; IM: Intermediate metabolizer; PM: Poor metabolizer; RM: Rapid metabolizer.

Table 6: AEs and SS among patients with duodenal ulcer.

Events	Anaprazole ($n = 220$)	Rabeprazole ($n = 219$)	Total ($n = 439$)	χ^2 or Fisher	*P*
AEs	74 (33.6)	84 (38.4)	158 (36.0)	1.06	0.30
SAEs	3 (1.4)	1 (0.5)	4 (0.9)	Fisher	0.62
TEAEs	72 (32.7)	84 (38.4)	156 (35.5)	1.52	0.22
Serious TEAEs	3 (1.4)	1 (0.5)	4 (0.9)	Fisher	0.62
TEAEs leading to discontinuation	3 (1.4)	0	3 (0.7)	Fisher	0.25
TEAEs leading to withdrawal	2 (0.9)	0	2 (0.5)	Fisher	0.50
TEAEs of special interest	3 (1.4)	4 (1.8)	7 (1.6)	Fisher	0.72
Drug-related TEAEs	18 (8.2)	24 (11.0)	42 (9.6)	0.98	0.32
Serious drug-related TEAEs	0 (0)	1 (0.5)	1 (0.2)	Fisher	0.50
Drug-related TEAEs of special interest	2 (0.9)	3 (1.4)	5 (1.1)	Fisher	0.69
Severity of drug-related TEAEs				Fisher	1.00
Mild	15 (6.8)	21 (9.6)	36 (8.2)		
Moderate	3 (1.4)	3 (1.4)	6 (1.4)		
Severe	0	0	0		

AE: Adverse event; SAE: Serious adverse event; SS: Safety set; TEAE: Treatment-emergent adverse event. Data are presented as *n* (%).

be unrelated to anaprazole. One (0.5%) SAE had occurred in the rabeprazole group and was considered to be possibly related to treatment and moderate in severity. Symptoms improved after drug withdrawal.

Most treatment-emergent adverse events (TEAEs) were mild and there was a numerically lower proportion of TEAE incidences with anaprazole (32.7%) than with rabeprazole (38.4%). The most common TEAEs according to SOC were gastrointestinal disorders (anaprazole, 10.9%; rabeprazole, 14.2%) and investigations (anaprazole, 9.5%; rabeprazole, 14.2%) [Table 7]. The most common TEAEs according to PT were diarrhoea (anaprazole, 1.4%; rabeprazole, 2.7%) and urinary tract infections (anaprazole, 2.3%; rabeprazole, 1.8%).

All TEAEs that led to treatment discontinuation occurred in the anaprazole group ($n = 3$ [1.4%]) and included one case each of dyspnoea (moderate severity) and diarrhoea (moderate severity) that were considered possibly related to the study drug, and one case of hyperhidrosis (mild severity) that was considered unrelated. TEAEs leading to study withdrawal occurred in two patients in the anaprazole group and included one case of dizziness (mild severity) considered unrelated to the study drug and one case of diarrhoea (moderate severity) considered possibly related.

Six AEs of special interest in five patients were judged to be related to the study drug. These included hepatic function abnormalities in four patients (anaprazole, $n = 1$ [0.5%]; rabeprazole, $n = 3$ [1.4%]) and hypothyroidism in one patient (0.5%) in the anaprazole group. Two cases of AEs of special interest, one in each group, were not related to the study drug. There were no AEs of QTc interval prolongation, no notable changes in vital signs, physical or laboratory examinations, or electrocardiograms, and no deaths.

Discussion

This comparison of rabeprazole and anaprazole, a novel PPI developed independently in China, revealed the non-inferior efficacy of anaprazole to rabeprazole in Chinese patients with duodenal ulcers after 4 weeks of treatment. The 4-week healing rate based on BICR of the endoscopy results showed that anaprazole was non-inferior to rabeprazole.

To reduce bias and control trial quality, the primary endpoint was evaluated by BICR as conducted in both

Table 7: TEAEs with an incidence of ≥1% by SOC and PT (SS) among patients with duodenal ulcer.

SOC/PT	Anaprazole (*n* = 220)	Rabeprazole (*n* = 219)	Total (*n* = 439)	χ^2 or Fisher	*P*-value
TEAEs	72 (32.7)	84 (38.4)	156 (35.5)	1.52	0.22
Gastrointestinal disorders	24 (10.9)	31 (14.2)	55 (12.5)	1.06	0.30
Diarrhoea	3 (1.4)	6 (2.7)	9 (2.1)	Fisher	0.34
Gastritis erosive	2 (0.9)	4 (1.8)	6 (1.4)	Fisher	0.45
Gastric polyps	0	6 (2.7)	6 (1.4)	Fisher	0.02
Duodenogastric reflux	3 (1.4)	2 (0.9)	5 (1.1)	Fisher	1.00
Gastric ulcer	1 (0.5)	3 (1.4)	4 (0.9)	Fisher	0.37
Abdominal distension	0	3 (1.4)	3 (0.7)	Fisher	0.12
Investigations	21 (9.5)	31 (14.2)	52 (11.8)	2.23	0.14
Alanine aminotransferase increased	4 (1.8)	2 (0.9)	6 (1.4)	Fisher	0.69
Urinary occult blood positive	3 (1.4)	2 (0.9)	5 (1.1)	Fisher	1.00
Tri-iodothyronine free increased	1 (0.5)	4 (1.8)	5 (1.1)	Fisher	0.22
White blood cells urine positive	1 (0.5)	3 (1.4)	4 (0.9)	Fisher	0.37
Protein urine present	1 (0.5)	3 (1.4)	4 (0.9)	Fisher	0.37
Infections and infestations	18 (8.2)	16 (7.3)	34 (7.7)	0.12	0.73
Urinary tract infection	5 (2.3)	4 (1.8)	9 (2.1)	Fisher	1.00
Upper respiratory tract infection	4 (1.8)	5 (2.3)	9 (2.1)	Fisher	0.75
Nasopharyngitis	4 (1.8)	0	4 (0.9)	Fisher	0.12
Cardiac disorders	4 (1.8)	9 (4.1)	13 (3.0)	2.01	0.16
Sinus bradycardia	2 (0.9)	4 (1.8)	6 (1.4)	Fisher	0.45
Nervous system disorders	6 (2.7)	5 (2.3)	11 (2.5)	0.09	0.77
Dizziness	4 (1.8)	3 (1.4)	7 (1.6)	Fisher	1.00
Hepatobiliary disorders	3 (1.4)	7 (3.2)	10 (2.3)	Fisher	0.22
Hepatic function abnormal	3 (1.4)	7 (3.2)	10 (2.3)	Fisher	0.22
Musculoskeletal and connective tissue disorders	4 (1.8)	2 (0.9)	6 (1.4)	Fisher	0.69
Arthralgia	3 (1.4)	1 (0.5)	4 (0.9)	Fisher	0.62
Blood and lymphatic system disorders	1 (0.5)	4 (1.8)	5 (1.1)	Fisher	0.22
Anaemia	0	3 (1.4)	3 (0.7)	Fisher	0.12
General disorders and administration site conditions	1 (0.5)	3 (1.4)	4 (0.9)	Fisher	0.37
Pyrexia	0	3 (1.4)	3 (0.7)	Fisher	0.12
Psychiatric disorders	0	3 (1.4)	3 (0.7)	Fisher	0.12
Insomnia	0	3 (1.4)	3 (0.7)	Fisher	0.12

PT: Preferred term; SOC: System organ class; SS: Safety set; TEAE: Treatment-emergent adverse event.

phase II and phase III studies.[11] These phase III findings build on those of the phase II trial that assessed 4-week ulcer healing rates of anaprazole or rabeprazole treatment by BICR.[11] The difference in the ulcer healing rate (−2.8%; 95% CI: −7.7%, 2.2%) was similar to that of the phase II study (−2.9%), confirming the findings of the phase II study in a larger patient population. The healing rate in the anaprazole group (93.3%, PPS) was within the range specified in the Chinese guidelines for peptic ulcer treatment (healing rate >90%).[16]

At 4 weeks of treatment, patients in both groups experienced substantial improvements in both overall and individual ulcer symptoms and had similar improvement rates. There were no statistically significant differences between treatments for time to elimination of ulcer-related or nocturnal abdominal pain.

The safety and tolerability profiles were similar between treatments. However, the frequency of AEs was slightly higher with rabeprazole than anaprazole. The phase II study revealed potentially improved liver tolerance with anaprazole *vs*. rabeprazole. This trend was also observed in this phase III study (abnormal liver function: anaprazole, 1.4%; rabeprazole, 3.2%). Nonetheless, this finding should be confirmed in larger studies (i.e., real-world studies). Previous studies have reported that symptoms in the digestive and nervous systems are the most common PPI-related AEs.[17-22] Similarly, both phase II and III studies of anaprazole reported gastrointestinal disorders as the most common AEs, and the incidence was numerically lower with anaprazole than rabeprazole.

Subgroup analysis showed that the healing rates in the *H. pylori*-positive and -negative subgroups were 92.2% and 85.4% (FAS), respectively, for patients treated with anaprazole. Although the difference in healing rates was not significantly different ($P = 0.29$), the rate was numerically lower in the *H. pylori*-negative group and may be explained by the significant difference in the

distribution of the maximum ulcer area between *H. pylori*-negative and -positive patients, considering the healing time.

Subgroup analysis also showed that the efficacy of anaprazole did not differ significantly by *CYP2C19* genotype status. *CYP2C19* genetic polymorphisms alter the pharmacokinetics and clinical efficacy of many PPIs. Omeprazole is metabolized primarily into its 5-hydroxy form by *CYP2C19* and, to a lesser extent, into sulfone metabolites by *CYP3A4*.[23-25] There is a 20-fold difference in omeprazole exposure between *CYP2C19* rapid extensive metabolizers and PMs.[26] Similar findings have been obtained for lansoprazole.[27,28] Pantoprazole undergoes O-demethylation via *CYP2C19*, followed by sulfate conjugation and sulfone/sulfide formation, which may be affected by *CYP2C19* genotype.[29] Unlike these PPIs, rabeprazole is metabolized through the formation of a thioether compound by non-enzymatic reduction of sulfoxide.[30] However, it is metabolized to desmethyl rabeprazole by *CYP2C19*. Significant differences in intragastric mean pH values, serum gastrin area under the curve (0–24 h), and plasma rabeprazole levels have been reported in patients with the three *CYP2C19* genotype.[10] An *in vitro* study has demonstrated that enzyme inhibition and induction between anaprazole and *P450* cytochromes were not observed in human liver microsomes (Xuanzhu Biopharmaceutical Co., Ltd., data on file). Therefore, the stability of the treatment effect and incidence rate of drug–drug interactions are better with anaprazole than other PPIs.

This study had some limitations. First, only Chinese patients were included, potentially limiting the generalizability of these findings. Second, this study lacked data for special groups such as hepatic and renal insufficiency, elevated thyroid stimulating hormone levels, and non-steroidal anti-inflammatory drug and anticoagulant use. Third, the healing rate was the only factor evaluated by *CYP2C19* genotype. Thus, pharmacokinetic and 24-h gastric acid studies evaluating the effects of the *CYP2C19* genotype are warranted.

Based on healing rates, anaprazole was non-inferior to rabeprazole for the treatment of duodenal ulcers after 4 weeks of treatment. There were no significant differences in the improvement rates of clinical symptoms or in the time-to-elimination of abdominal or nocturnal abdominal pain between the treatments. *CYP2C19* polymorphisms and the *H. pylori* infection status did not affect efficacy outcomes. Anaprazole demonstrated a favorable safety profile. The observed potential advantages of anaprazole in reduced gastrointestinal AEs and improved liver tolerance should be confirmed in larger studies.

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Conflicts of interest

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