Comparison of Vonoprazan fumarate-based Triple Therapy Versus Proton Pump Inhibitor and Bismuth Based Quadruple Therapy in the Eradication of Helicobacter Pylori: A Single-center Prospective Open-label Controlled Study

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Main researcher: Tang Yanliu

Research Organization: Third Xiangya Hospital, Central South University

Contract Research Organization: None

Declaration of secret

The confidential information about the trial involved in this program belongs to Third Xiangya Hospital, Central South University and is reviewed only by the researchers of this clinical trial, the ethics committee and the supervision and administration department of medical institutions. Without written permission from Third Xiangya Hospital, Central South University, it is strictly prohibited to disclose to unrelated organization.

Proposal Signing Page

The principal investigator agrees:

I confirm that I have read and understood this program and any other supporting information. I agree to conduct this study in accordance with the requirements of this program, while respecting the rights, safety, privacy, and health of the subjects of the study, and in accordance with:

- Ethical principles in the Helsinki Declaration.
- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use /E6.
- All applicable laws and regulations in China, including but not limited to laws and regulations regarding privacy protection and disclosure of clinical trials.
- Regulatory requirements for reporting serious adverse events.

Third Xiangya Hospital, Central South University

Main Researcher Signatures: 唐岸柳

Date: 23, May 2021

Program abstract

The name of the scenario	Comparison of Vonoprazan fumarate-based Triple Therapy Versus Proton Pump Inhibitor and Bismuth Based Quadruple Therapy in the Eradication of Helicobacter Pylori: A Single-center Prospective Open-label Controlled Study
Version number	1.3
date	2021-05-16
The bidder	Department of Gastroenterology, Third Xiangya Hospital, Central South University
Indications	Diagnosed with Hp infection
The purpose of the experiment	Compare the four treatments [(1) Vonoprazan fumarate + amoxicillin + doxycycline, (2) Vonoprazan fumarate + furazolidone + doxycycline, (3) esomeprazole + colloidal bismuth tartrate + amoxicillin + doxycycline, and (4) esomeprazole + colloidal bismuth tartrate + furazolidone + doxycycline] for Helicobacter pylori (hereafter referred to as Hp), and assess the effectiveness, safety, drug compliance, and socioeconomic evaluation.
experimental design	A single-center, prospective, open-label, parallel control design was conducted to enroll 596 patients with confirmed Helicobacter pylori infection. Patients were randomly divided into four groups, respectively accept four treatment regimens including (1) Vonoprazan fumarate + amoxicillin + doxycycline, (2) Vonoprazan fumarate + furazolidone + doxycycline, (3) esomeprazole + colloidal bismuth tartrate + amoxicillin + doxycycline, and (4) esomeprazole + colloidal bismuth tartrate + furazolidone + doxycycline. The effectiveness, safety and compliance of the four regimens were compared, and the cost-benefit analysis of the different regimens was conducted. The purpose of this study was to explore the most appropriate treatment plan for radical treatment of Helicobacter pylori.
Total number of cases	596 cases are planned for the group
Number of research	Single center

centres	
The duration of the study	2021-06-17～2022-06-17
Case selection criteria and exit criteria **Case selection criteria and exit criteria**	**Group criteria:** 1. The age ≥ 18 and ≤ 80 2. The Urea Breath Test (UBT) tested positive for Hp infection 3. Anti-Hp therapy without any treatment 4. Have a gastroscopy within 1 month 5. Clearly understand, volunteer to participate in the study and sign an informed consent form by himself **Exclusion criteria:** Subjects who meet any of the following criteria cannot be selected for this test: First, the patient's physical condition cannot accept Hp eradication treatment 1. Allergic to the drugs used in this clinical study 2. Use of PPI, histamine H2 receptor antagonists, antibiotics, palladium, probiotics, or antibacterial drugs before 4 weeks of treatment 3. Use adrenal corticosteroids, nonsteroidal anti-inflammatory drugs and anticoagulants 4. Diseases or clinical conditions that may interfere with research and treatment assessment, such as liver disease, cardiovascular disease, lung disease, kidney disease, metabolic disease, mental illness, or malignant tumors 5. Pregnant or lactating women 6. Participate in other clinical studies before 3 months Second, do not agree to participate in this study Third, there are other problems that do not meet the requirements of this study or affect the results of the study: 1. Suspected history of antibiotic abuse 2. Brain injury, mental illness or epilepsy, etc. can not communicate with patients or other diseases that may affect follow-up **Termination criteria:** If the subject meets any of the following criteria, the researcher will discontinue the study early: 1. An allergic reaction to the drug or other component used in this clinical trial 2. Existence of a adverse event, the researchers

	determined that the study needed to be terminated early because continued participation in the study may pose an unacceptable risk to the subject's health, or because the subject was reluctant to continue the study because of the adverse event **Exit criteria:** If the subject meets any of the following criteria, the patient will withdraw from the study: 1. The subject withdrew his informed consent 2. The subjects were not interviewed. During the study period, when the subjects meet the above suspension/exit criteria, the researcher can terminate the participation and should follow up in medical procedures. The reason and date of the subject's withdrawal must be recorded in the case report form and the original information.
Research steps	**Research steps:** 1. Informed consent and patient screening: Inform the patients in the proposed group of the specific content of this study and possible risks. All patients in the group or the authorized trustees of the patients need to sign the informed consent form, and then in accordance with the selection criteria and exclusion criteria, a single center selected confirmed infection of Hp patients (about 596 cases). 2. Collect patient information: including initials, gender, age, outpatient number, hospitalization number, date of entry, education, occupation, smoking, alcohol consumption and gastroscopy results (ulcers, atrophic gastritis, tumors, etc). 3. Random Grouping: A table of random numbers pre-generated with SPSS20.0 and divided it into four groups of 1:1:1:1. The treatment plan is determined by the random number of randoms drawn by the patient, and the random process is done by the specified study designer. 4. Eradication treatment: four groups of patients received Vonoprazan fumarate + amoxicillin + doxycycline, Vonoprazan fumarate + furazolidone + doxycycline, esomeprazole + colloidal bismuth tartrate + amoxicillin + doxycycline, and esomeprazole + colloidal bismuth tartrate + furazolidone + doxycycline 5. Follow-up: Each patient receives two follow-ups. The first follow-up is conducted on the first day after the patient has concluded eradication treatment, and the follow-up is to evaluate the patient's drug compliance and whether

	adverse reactions occurre. Basing on the patient's actual situation, determine whether the patient needs other treatment. The second follow-up is 4-8 weeks after the patient had discontinued proton pump inhibitors, vonoprazan fumarate, and antibiotics. At this point, the researchers reminded the patient to undergo a urea exhalation test and determine whether the patient had succeeded in eradicating HP. 6. Remedy: If the patient finds failure on the second follow-up, he will receive treatment different from the previous treatment and be followed up again at 14^{th} days after taking the drug and one month after discontinuation. If the second treatment fails, the drug will be discontinued for half a year, and after six months, the patient will be treated in a different way. Remedy after adverse reactions: immediately discontinue medication and go to the hospital in time if symptoms are severe. According to the corresponding symptoms， give support treatment including but not limited to rehydration, anti-inflammatory anti-allergy, anti-shock treatment. 7. Collect information on treatment effectiveness and cost of treatment: Record study participants reviewing UBT trial results, adverse reactions in medication, drug compliance, and total drug costs.
Observe the indicator	**Key evaluation indicator** eradication rate **Minor evaluation indicators:** 1. Drug compliance 2. Rate of all types of adverse events 3. Cost-benefit analysis
Security metrics	Incidence of adverse events/severe adverse events/suspected unanimity serious adverse events.
Statistical analysis **Statistical**	1. **Sample size calculation:** Refer to previous studies, the Hp eradication rate of triple therapy containing Vonoprazan fumarate was 91.4%, and the hp eradication rate of quadrol therapy containing proton pump inhibitors and colloidal tartaric acid was 81.3%. Assuming a 90% certainty, the α is 0. 05 (two-sided), a total of 476 patients are required, assuming a follow-up loss of 20% and a planned sample size of 596 patients (149 patientsper group) [1-6]. 2. **General principles:** The adoption rate (%) and mean ± standard deviations

analysis	to the classification variables and continuous variables for standard descriptive statistics. The classification variable comparison is based on the square test, and the continuous variable comparison uses the two-sample t-test. 3. **Demographics and baseline characteristics:** Summarize all demographic variables and baseline characteristics. Continuity variables are used for descriptive statistics, and classification variables are calculated in frequency and percentage ratios. 4. **Evaluation and security indicators:** Analysis of demographic data, baseline characteristics, Hp eradication, and drug compliance. Statistics the incidence of adverse events/severe adverse events/suspected unanimity serious adverse events. Using the Markov model, the cost-effectiveness of treating HP in different treatment options is analyzed and the best cost-effective solution is selected. This study does not conduct interim analysis.

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1. Background of the study

1.1 The current situation of research at home and abroad

Helicobacter pylori (Hp)infection is one of the most common chronic infections in humans. Epidemiological surveys show that more than half of the world's natural population has Hp infection, more than almost all chronic infectious diseases, and infection rates are generally higher in developing countries than in developed countries. China is one of the countries with a high incidence of Hp infection, and epidemiological surveys show that the prevalence of Hp infection in China is 42% to 64%. Given our large population base, China is probably the most infected country in the world, so Hp infection and related diseases are serious health problems [7, 8].

Hp infection is generally difficult to remove spontaneously leading to lifelong infection, unless eradication treatment, or stomach mucosa in severe intestinal metaplasia. Hp infections are closely related to the occurrence of chronic active gastritis, peptic ulcers, gastric mucosa-related lymphoma (MALT) lymphoma and stomach cancer and were defined as Class I carcinogens by the World Health Organization / International Agency for Research on Cancer

in1994[1]. In 2018, the range of indications that detect the presence of Hp infections will be significantly expanded. In 2020, the Taipei Global Consensus emphasizes the role of eradicating Hp in achieving the goal of reducing or eliminating stomach cancer[11].

Eradication of Hp can prevent the recurrence of peptic ulcers and reduce the risk of gastric cancer. Although many studies and consensus conferences have provided treatment recommendations that are considered the latest [12, 13], compared with other infectious diseases, the overall treatment success of H. pylori is still very low [14]. There are many different therapies for the treatment of Hp, including triple therapy consisting of proton pump inhibitors, amoxicillin and clarithromycin, metronidazole, fluoroquinolone or rifabutin; bismuth quadruple therapy; proton pump inhibition Drug and amoxicillin dual therapy and a group of 4 drug treatments consisting of proton pump inhibitors, amoxicillin, clarithromycin, and metronidazole. Despite 30 years of treatment experience in the world, the ideal H. pylori eradication program is still unclear, and H. pylori treatment cannot avoid the increase in global antimicrobial resistance. The efficacy of triple therapy combining proton pump inhibitors and two antibiotics (amoxicillin and clarithromycin) is gradually decreasing, from 95% to 80% globally and from 89% to 78 % in China % [15, 16] . Since then, quadruple therapy has gradually replaced triple therapy as the first-line treatment for Hp infection [17]. In China, bismuth-containing quadruple therapy is highly recommended as the first-line treatment for Hp infection. Although the eradication rate has increased, the therapy still has limitations, including bismuth-related side effects, poor patient compliance with medications, high resistance to clarithromycin and metronidazole, and high drug costs. In addition, PPI often exhibits problems such as slow onset of action and large inter-individual variability [18]. Therefore, there is an urgent need to study a new alternative therapy.

1.2 Basis for project establishment

In recent years, a new antisecretory drugs - potassium ion competitive acid blockers are introduced, these drugs and K + competition H +, K + - ATP enzyme (proton pump) binding sites on cells thus inhibiting the secretion of stomach acid Compared with PPI drugs, H+ and K+-ATPase can be inhibited without acid activation, and the acid suppression effect is not affected by CYP2C19 gene polymorphism. Its novel mechanism of action and unique

pharmacokinetic characteristics make it show better characteristics than PPI, such as fast onset, stable structure, long-lasting acid suppression effect, small individual differences, and fewer adverse reactions [19].

As its representative drug, vonoprazan fumarate green tablets were launched in Japan in 2015 and are mainly used to treat acid-related diseases, including reflux esophagitis, gastric ulcer, and duodenal ulcer. In 2019, vonoprazan fumarate green tablets were approved by the U.S. Food and Drug Administration (FDA) as triple combination with amoxicillin and clarithromycin, or double combination with amoxicillin for the treatment of Hp infection. Several clinical studies have shown that vonoprazan fumarate raw tablets are safe, effective, and well tolerated in the treatment of reflux esophagitis and eradication of Hp [20]. A network meta-analysis of published randomized controlled trials found that in the first-line empirical treatment of Hp infection, the triple therapy of vonoprazan fumarate tablets achieved a high eradication rate of more than 90%, while the standard triple therapy was the most ineffective therapy [21]. However, unfortunately, although the analysis showed that the triple therapy of vonoprazan fumarate green tablets performed well, Japan's clarithromycin resistance is very high, resulting in a decline in the effectiveness of the therapy, with a reported cure rate of <90% [22]. According to reports, in the presence of clarithromycin resistance, the cure rate is about 80%, so most patients (estimated at 88%) receive clarithromycin unnecessarily, which leads to global antibiotic resistance [23]. In areas with high clarithromycin resistance, a recent study in Japan found that [3] Wonoprazan - Amoxicillin dual therapy achieved a Hp eradication rate like Wonuo's triple therapy. However, although this program has the smallest type, the smallest dose, and the shortest course of treatment, the adverse reactions caused by the excessive dose of amoxicillin limit the use of this program. Therefore, this program is generally used for salvage treatment. We are trying to find other therapies based on vonoprazan fumarate green tablets that can be used as a first-line solution for Hp eradication.

As a developing country with a high incidence of Hp infection and relatively insufficient medical resources in some regions, the Hp infection eradication treatment program

applicable in China needs to consider both effectiveness and efficiency. 2017 Nian Fifth National Consensus on treatment of Helicobacter pylori infection [7] concerning the eradication of Hp treatment, the recommended PPI + bismuth + 2 antibiotics scheme fifth national consensus report Helicobacter pylori infection treatment, antibiotic amoxicillin is recommended, Clarithromycin, metronidazole, levofloxacin, tetracycline and furazolidone. In recent years, studies have found that the resistance rate of Hp to clarithromycin, metronidazole, and levofloxacin (fluoroquinolones) is on the rise, with double, triple or more resistance. Contrary to the high resistance rate of the above three antibiotics, the resistance rate of Hp to amoxicillin (0%~5%), tetracycline (0%~5%) and furazolidone (0%~1%) is still very low in China. [7, 24, 25]. World Gastroenterology Organization developing countries issued Hp global guidelines state that in Hp infection high, relatively resource-poor developing countries, furazolidone price of the most affordable in all alternative antibiotics, the resistant rate is also very low, at Hp It has an important position in the eradication treatment of infection [26]. Tetracycline has many adverse reactions due to liver and kidney function damage, and it is difficult to be widely promoted in clinical practice. As a semi-synthetic tetracycline, doxycycline has the same antibacterial mechanism as tetracycline, and its antibacterial effect is 2 to 4 times stronger than tetracycline. Doxycycline can be completely absorbed by oral administration and is not affected by food. Its half-life is if 16 hours in the body. Doxycycline is metabolized in the liver and is mainly excreted through the kidneys. However, when renal function is impaired, gastrointestinal excretion becomes the main excretion pathway. It can be used for patients with renal insufficiency and is the least toxic kind of tetracycline antibiotics.

Therefore, this study chose four treatment options: triple therapy based on Vonoprazan fumarate + amoxicillin + doxycycline, Vonoprazan fumarate + furazolidone + doxycycline, and PPI and bismuth-based quadruple therapy - esomeprazole + colloidal bismuth tartrate + amoxicillin + doxycycline, esomeprazole + colloidal bismuth tartrate + furazolidone + doxycycline. Considering the main result, the objectivity of the detection of Hp eradication rate, the open-label design is unlikely to bias the results. We carry out a single-center, prospective, open-label clinical controlled study for the eradication of Hp infection to evaluate

the effectiveness of the four treatment options, the incidence of adverse events, patient compliance and economic benefits. Trying to determine whether triple therapy based on vonoprazan fumarate tablets can be used as a first-line treatment to eradicate Hp in Chinese patients, thereby improving clinical outcomes, improving patient compliance, avoiding unnecessary side effects, and reducing the incidence of Hp infection the cost of.

2. Research purposes

Comparison of four treatment options for radical treatment of Hp (F (1) Vonoprazan fumarate + amoxicillin + doxycycline, (2) Vonoprazan fumarate + furazolidone + doxycycline, (3) esomeprazole + colloidal bismuth tartrate + amoxicillin + doxycycline, and (4) esomeprazole + colloidal bismuth tartrate + furazolidone + doxycycline), to evaluate the effectiveness, safety, and patient compliance of the four regimens, And socioeconomic evaluation.

3. Subjects

Inclusion criteria:

1. Age≥ 18 years old, ≤ 80 years old

2. Urea breath test (UBT) test is positive for Hp infection.

3. Anti-Hp therapy without any treatment

4. Gastroscopy within 1 months

5. Clearly understand, volunteer to participate in the study and sign an informed consent form by himself

Exclusion criteria:

Subjects who meet any of the following criteria may not be selected for this test:

First, the patient's physical condition cannot accept Helicobacter pylori root treatment:

1. Allergic to the drugs used in this clinical study.

2. Use PPI, histamine H2 receptor antagonist, antibiotics, bismuth, probiotics, or drugs with antibacterial effect within 4 weeks before study treatment.

3. Use adrenal corticosteroids, non-steroidal anti-inflammatory drugs, and anticoagulants.

4. There are diseases or clinical conditions that may interfere with the evaluation of research and treatment, such as liver disease, cardiovascular disease, lung disease, kidney

disease, metabolic disease, mental disease, or malignant tumor.

5. Pregnant or lactating women.

6. Participate in other clinical studies within 3 months before the registration of this clinical study.

Second, do not agree to participate in this study

Third, there are other problems that do not meet the requirements of this study or affect the results of the study:

1. Suspected history of antibiotic abuse

2. Patients with craniocerebral injury, mental illness, or epilepsy, etc. unable to communicate with patients or other diseases that may affect follow-up

Termination criteria:

If the subject meets any of the following criteria, the researcher will suspend the study early:

1. Allergic reactions to the drugs or other components used in this clinical trial

2. In the event of an adverse event, the investigator judges that the study needs to be terminated early, because continuing to participate in the study may bring unacceptable risks to the health of the subject, or the subject is unwilling to continue participating in the study due to adverse events

Exit criteria:

If the subject meets any of the following criteria, the patient will withdraw from the study:

1. Subject withdrew informed consent
2. Subject was lost to follow-up.

During the research period, when the subject meets the above suspension / withdrawal criteria, the researcher can terminate the subject's participation, and should try to follow medical routines for subsequent treatment and follow-up. The reason and date of the subject's withdrawal must be recorded in the case report form and original data.

4. Research and design

4.1 Design principle

This trial adopts a single-center, prospective, open-label parallel control design. It is planned to enroll 596 patients with confirmed Hp infection; the patients were randomly

divided into four groups and received Vonoprazan fumarate + furazolidone + doxycycline. Plan, vonoprazan fumarate + Amoxicillin + Doxycycline Plan, Esomeprazole + Colloidal Bismuth Tartrate + Furazolidone + Doxycycline Plan, and Esomeprazole + Colloidal Tartaric Acid Bismuth + amoxicillin + doxycycline regimen. Compare the effectiveness, safety, and patient compliance of the four programs, and conduct cost-benefit analysis of different programs at the same time. The purpose of this trial is to find the most suitable treatment plan for the radical cure of Hp.

4.2. Open label design and random grouping

Due to the obvious differences between the different groups of drugs, clinicians and patients will inevitably know the status of patients taking drugs, so this trial adopts an open-label design. To this end, we have set up a non-blind team and a blind team. The non-blind team includes all researchers who need access to randomization information and do not participate in the evaluation, including researchers who randomize patients, who are responsible for diagnosis and Physician who prescribes medicine. The blinded research team is a researcher who participates in subject follow-up, safety evaluation, data collection and analysis. During the entire trial process, unblinded researchers are not allowed to disclose any information and documents related to drug grouping to any blinded personnel, subjects, and sponsors. Any relevant documents related to drug grouping should be kept separately by authorized non-blind researchers, and irrelevant personnel should not be contacted at will to avoid breaking blindness.

With the help of SPSS20.0 software, a random number table is generated in advance, and it is divided into four groups 1:1:1:1, corresponding to four radical cure programs. According to the random number assigned to the patient, the radical treatment plan is determined.

5. Test steps:

5.1 Informed consent with patient screening

Firstly, inform the patients who are to be enrolled about the study, including the source, purpose, significance, and possible benefits and risks of participating in the study. After the patients have a complete understanding of the study, they can decide by themselves whether to participate. If the patient voluntarily participates, they sign the informed consent form and the investigator also signs. According to the inclusion and exclusion criteria, the single center selected 596 eligible patients.

5.2 Collect patient-related information

Collect patient-related information, including initials, gender, age, outpatient number, hospitalization number, enrollment date, education, occupation, smoking status, drinking status; height, weight, other comorbid diseases, whether close contacts have Hp infection, Results of gastroscopy and laboratory tests. The result of gastroscopy is whether ulcers, atrophic gastritis, etc. are found.

5.3 Random grouping

Use the random number table generated in advance by SPSS20.0 software and divide it into four groups 1:1:1:1. According to the random number drawn by the patients, the radical treatment plan is determined. The random process is completed by the study designer.

5.4 Eradication treatment

The patients were randomly divided into four groups (Group1, Group2, Group3, Group4) according to 1:1:1:1 and were treated with Hp eradication for 14 days according to the course of treatment. All study patients received instructions and were required to take the medication strictly and regularly. Record the time of first treatment and the time of termination of treatment.

Table 1: Four treatment options included in the study

	Group1	Group2	Group3	Group4
Esomeprazole (5mg, 2 times /d, orally half an hour before meals)	√	√		
Colloidal bismuth tartrate (220mg, 2 times /d,	√	√		

orally half an hour before meals)				
Amoxicillin (1000mg, 2 times /d, orally after meals)	√		√	
Furazolidone (100mg, 2 times /d, orally after meals)		√		√
Doxycycline (100mg, 2 times /d, orally after meals)	√	√	√	√
vonoprazan fumarate (20 mg, 2 times /d).			√	√

5.5 Follow-up

Each patient will be followed up twice. The first follow-up is on the first day after the patient ends the eradication treatment. The content of the follow-up is to evaluate the patient's drug compliance and whether adverse reactions have occurred. According to the actual situation of the patient, determine whether the patient needs to continue to receive other treatments. The second follow-up was 6-8 weeks after the patient stopped using proton pump inhibitors, fumarate, and antibiotics. The researcher reminded the patient to accept a UBT test at this time and judge whether the patient successfully eradicated Hp.

5.6 Remedial measures

5.6.1 Remedy for failure to eradicate

If the patient finds that no radical cure is successful at the second follow-up visit, he will receive a treatment that is different from the previous radical cure plan and follow up again after taking the drug for 14 days and one month after stopping the drug. If the second radical cure fails, the drug will be discontinued for half a year, and after half a year, the patient will receive a different treatment from the previous two radical cures.

5.6.2 Remedies after adverse reactions: Certain adverse reactions may occur during the use of study drugs. We will inform patients in detail of the adverse reactions and precautions in medication (Table 2). When an adverse reaction occurs, our remedy measures are as follows and inform the patient: stop the drug immediately and go to the hospital for treatment if the symptoms are severe. Symptomatic and supportive treatment based on corresponding symptoms, including but not limited to fluid replacement, anti-inflammatory and anti-allergic, anti-shock, and other treatments.

Table 2 Adverse reactions and precautions of study drugs

	adverse reactions	Precautions
Essomelazole	Whole body: abdominal swelling, allergic reactions, fatigue, back pain, chest pain, pain under the breastbone, facial edema, peripheral edema, hot flashes, fatigue, fever, flu-like symptoms, generalized edema, leg edema, discomfort, pain, chills: Cardiovascular: flushing, hypertension, tachycardia. Endocrine: Goiter. Gastrointestinal tract: abnormal bowel function, constipation, dyspepsia, dysphagia, gastrointestinal dysplasia, upper abdominal pain, belching, esophageal disease, frequent stools, gastroenteritis, gastrointestinal bleeding, gastrointestinal symptoms (non-specific), hiccups, melena, oral disease, pharyngopathy, rectal disease, increased serum gastrin, tongue disease, tongue edema, ulcerative stomatitis, vomiting, gastrointestinal candidiasis, clostridium difficile Diarrhea, pancreatitis, bilirubinemia, abnormal liver function; Hearing: earache, tinnitus. Immune system: immediate allergic reaction/shock. blood system: anemia, hemoglobin reduction anemia, cervical lymphadenopathy, snoring, leukocytosis, leukopenia, thrombocytopenia. Metabolism/Nutrition: Diabetes, hyperuricemia, hyponatremia, elevated alkaline phosphatase, thirst, vitamin B12 deficiency, weight change. Musculoskeletal system: joint pain, worsening arthritis, arthropathy, cramps, anal pruritus, skin rash, erythema, maculopapular rash, skin inflammation, increased sweating, urticaria. Feelings: otitis media, perverted sense of smell, loss of taste, perverted sense of taste, blurred vision, Urogenital system: abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, frequent urination, candidiasis, genital candidiasis, polyuria.	Prohibited for drug allergies The lowest dose and shortest course of treatment suitable for the treatment situation. It may increase the risk of fractures of the hip, wrist or spine caused by osteoporosis. It is expected that PPI therapy needs to be extended or combined with drugs such as digoxin or drugs that can cause magnesemia (eg, diuretics). Medical professionals may consider monitoring the blood magnesium concentration before starting PPI therapy and regularly. Accompanied by rare genetic diseases, patients with glucose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase deficiency should not take this product Patients who have been treated with the drug for a long time (especially those treated for more than 1 year) should be monitored regularly. There may be a decrease in the absorption of vitamin B12 due to decreased penicillin or skin deficiency. Therefore, in long-term treatment, for patients with reduced body expansion or risk factors for reduced vitamin B12 absorption, this risk needs to be considered.
Colloidal tartare	The mouth may smell of ammonia, the tongue coating and stool are gray-black, nausea, and constipation	Drug allergies are forbidden; cannot be taken with milk and antacids at the same time
Amoxicillin	Diarrhea, indigestion, nausea, vomiting, urticaria and erythema	Drug allergies are forbidden; those with liver and kidney dysfunction/creatinine clearance less than 30 ml/min should be used with caution; those with anticoagulants should be used with caution.

Furazolidone	Nausea, vomiting, diarrhea, headache, dizziness, drug-heat rash, anal itching, asthma, orthostatic hypotension, hypoglycemia, lung infiltration, hemolytic anemia, jaundice, polyneuritis	Disabled for drug allergies; disabled for glucose-6-phosphate dehydrogenase deficiency; forbidden to drink alcohol; not suitable for patients with ulcer disease or bronchial asthma
Doxycycline	Nausea, vomiting, abdominal pain, diarrhea, liver toxicity, pancreatitis, allergic reactions (macro papules and erythema, urticaria, angioedema, allergic purpura, pericarditis and systemic lupus erythematosus skin lesions, exfoliative dermatitis, Anaphylactic shock and asthma) blood system (hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia); central nervous system (headache, vomiting, optic nerve head edema) double infection; reduction of normal flora in the body , Vitamin deficiency, fungal reproduction (dry mouth, pharyngitis, angular cheilitis and glossitis)	The drug is disabled for allergies
Vonoprazan fumarate	Diarrhea, constipation, nausea, and bloating. Headache, rash, edema, eosinophilia, liver toxicity, jaundice, skin, and subcutaneous diseases such as erythema multiforme	Drug allergies are prohibited; patients who are receiving atazanavir or rilpivirin are contraindicated

5.7 Cost indicator collection:

Collect the relevant expenses of the radical treatment plan, excluding outpatient expenses and depreciation expenses of testing, excluding indirect costs such as wage losses, transportation expenses, and hidden costs (physical and mental pain and loss caused by patients and family members).

5.8 Combined medication

The subjects' use of any drug other than the study drug is a combination drug, and all drug treatments used by the subject within 7 days before randomization and throughout the study must be recorded in the case report form (CRF). The study drug may interact with other drugs or things (Table 3), so other drugs that interact with the study drug are prohibited as much as possible during the study period.

Table 3: Study the combined drug interactions of drugs

	Drug/food interactions
Esomeprazole	Omeprazole (esomeprazole is its enantiomer) can interact with some reversal antiviral drugs (atazanavir, nelfinavir), so combined therapy is not recommended.

	It can inhibit gastric acid secretion. Therefore, for drugs whose bioavailability is greatly affected by gastric pH (such as ketoconazole, itraconazole, atazanavir, iron salts and digoxin), esomeprazole Can affect its absorption. Be cautious or prohibit other drugs related to the metabolism of CYP2C19 and CYP3A4 (such as diazepam, citalopram, imipramine, clomipramine, phenytoin, voriconazole, cilostazol, rifampin, Hypericum perforatum, etc.). Co-administration with tacrolimus can lead to an increase in the blood concentration of tacrolimus. The decrease in gastric acid caused by the drug can lead to the proliferation of intestinal chromaffin-like cells and the increase of chromogranin A levels, thus interfering with the examination of neuroendocrine tumors. Combined use with methotrexate may increase the serum concentration of methotrexate and/or its metabolites.
Colloidal bismuth tartrate	Milk and antacids can interfere with the effect of this product and should not be taken at the same time. Taking tetracycline together will affect the absorption of the latter. If it is used at the same time with other drugs, drug interactions may occur. For details, please consult your physician or pharmacist.
Amoxicillin	This product may reduce the effect of oral contraceptives; it is not recommended to use probenecid or allopurinol in combination.
Furazolidone	Combination with tricyclic antidepressants can cause acute toxic psychosis and should be avoided. Can enhance the effect of levodopa. Sympathomimetic amines, foods rich in tyramine, appetite suppressants, monoamine oxidase inhibitors, etc. can enhance the effect of this product.
Doxycycline	This product can inhibit the activity of plasma prothrombin, so patients receiving anticoagulant therapy need to adjust the dose of anticoagulant. When barbiturates, phenytoin or carbamazepine are used together with this product, the above-mentioned drugs can reduce the blood concentration of doxycycline due to the induction of microsomal enzyme activity, so the dose of doxycycline must be adjusted.
Vonoprazan fumarate	Should not be taken with atazanavir or rilpivirin, be cautious with nelfinavir, itraconazole, tyrosine kinase inhibitors (gefitinib, nilotinib, erlotinib), Take caution with digoxin and methyldigoxin, and take caution with CYP3A4 inhibitor clarithromycin

6. Results Evaluation index

6.1 Main evaluation indicators: Hp eradication rate

6-8 weeks after the end of the eradication treatment, a UBT test is performed to determine whether Hp is eradicated. During this period, no antibacterial drugs, bismuth, or PPI are taken. Use ITT analysis and PP analysis.

6.2 Secondary results

1. Medication compliance Use the MMAS scale to judge medication compliance. The full scale of the scale is 8 points, a score of < 6 is considered poor compliance, a score of 6-8 is

considered moderate compliance, and a score of 8 is considered good compliance.

2. The incidence of adverse events Adverse events include but are not limited to allergic reactions and shock, constipation, nausea, dizziness, diarrhea, and other adverse symptoms.

3. Drug costs The drug costs of the two treatment plans are calculated according to the 2021 Drug Pricing Catalogue of Changsha City. The price is expressed in U.S. dollars, and the renminbi is converted into U.S. dollars at the exchange rate reported in 2021: US $ 1.00 = 6.4962 CNY. According to the HP eradication rate, the Markov model is used to conduct a cost-benefit analysis of the two methods to determine which method is more cost-effective from an economic point of view

7. Security metrics:

The incidence of adverse events/serious adverse events/suspected unexpected serious adverse events.

1. Adverse events (AE) refer to adverse medical events that occur after subjects sign informed consent in clinical trials, but they may not be causally related to study drugs or research procedures. Therefore, adverse events can be any adverse or undesirable symptoms, signs, or diseases, including adverse drug events, important laboratory abnormalities, new diseases that appear during the study, and so on. For possible adverse events in this trial, refer to the "Test Procedures-Remedial Measures, Adverse Events" section.

2. A serious adverse event (SAE) refers to an adverse event that occurs during the research process after the subject has signed the informed consent form, and it meets one or more of the following criteria:

- lethal
- Life-threatening
- Lead to hospitalization or prolonged hospital stay
- Cause significant or permanent disability/loss of function
- Cause congenital abnormalities or birth defects
- Serious medical incident

3. Suspected unanticipated serious adverse events (SUSAR) are defined as: all unanticipated and serious adverse events that occur during the clinical trial that are related to

or suspicious of the trial operation process.

4. The causal relationship between the research procedure and the event can be divided into positively related, possibly related, possibly related, positively related, and impossible to judge.

• Relevant: the time of the reaction conforms to the time sequence of the test, and the reaction conforms to the known reaction type of the test. After the test is stopped, it will be improved, and if the test is continued, it will appear again.

• Possibly related: the time of occurrence of the reaction conforms to the chronological order of the test, the reaction conforms to the known reaction type of the test, and the patient's clinical state or other treatment methods may also produce the reaction.

• Possibly irrelevant: The response time does not match the chronological order of the test, the response does not match the known response type in the test, and the patient's clinical state or other treatment methods may also produce the response. The possibility cannot be ruled out and tested.

• Irrelevant: the time of the reaction does not match the chronological order of the test, and the reaction has a response type that is not known from the test. The patient's clinical state or other treatment methods may also produce the response, the disease state improves or the response is eliminated by stopping other treatments, Repeated use of other treatment methods appears, which is closely related to other risk factors.

• Unable to determine: the time of the reaction has no clear relationship with the time sequence of the test. The reaction is like the known reaction type in the test. Other drugs used at the same time may also cause the same reaction. There is no sufficient basis for judgment.

8. Statistical methods

8.1 sample size calculation:

With reference to previous studies, the Hp eradication rate of triple therapy containing vonoprazan fumarate was 91.4%, and that of quadruple therapy containing proton pump inhibitor + colloidal bismuth tartrate was 81.3%. Assuming 90% power, α is 0.05 (bilateral), a total of 476 patients are required, assuming a follow-up loss of 20%, and the planned sample size is 596 patients (149 patients in each group) [1-6].

8.2 General Principles:

The eradication rate (%) and mean ± standard deviation was used to perform standard descriptive statistics on categorical and continuous variables. The comparison of categorical variables uses the chi-square test, and the comparison of continuous variables uses the two-sample t test. According to the eradication rate and treatment cost, a Markov model was constructed, and the cost-benefit analysis of different treatments was carried out.

8.3 Demographics and baseline characteristics:

S Summarize all demographic variables and baseline characteristics (such as gender, age, education, occupation, smoking, drinking, and other comorbidities of the patient, etc.). Descriptive statistics (number of subjects, average, standard deviation, minimum, median, and maximum) were used for continuous variables, and categorical variables were used to calculate frequency and percentage rate.

8.4 Evaluation indicator:

The Hp radical cure rate and medication compliance were compared among the four groups of patients.

Statistic the incidence of adverse events/serious adverse events/suspected unexpected serious adverse events.

Analyze the relationship between demographic data and Hp eradication.

The Markov model is used to analyze the cost-effectiveness of different treatment options for the treatment of Hp and choose the best cost-effective option.

8.5 Subject Distribution:

Summarize and describe the screening of the subjects, the enrollment, the completion of the study, the reason for the screening failure, and the reason for early withdrawal. Summarize and describe the case distribution of each data set, the removal of each analysis set, and the reasons for the removal, etc. Summarize and describe the violation of at least one important plan.

8.6 Security Analysis:

SS set is used to analyze the security. According to the SOC/PT summary of the cases of adverse events during the trial, the number and incidence of adverse events and other occurrences were summarized. If there are multiple adverse events in the same subject, it is

counted as 1 case when calculating the incidence; when the subject has the same AE multiple times, it is counted as 1 case in the calculation of the incidence of the AE. Severity of AE: If multiple AEs occur in the same subject, the most severe AE will participate in the analysis; when the subject has multiple AEs, the most severe one will participate in the analysis of the severity of the AE. Provide a list of cases in which adverse events have occurred.

9. The research process

Table 4 Clinical Research Process Table

Project	The screening period	Treatment period		Follow-up period	
	Day -6 to 0	Week 1	Week 2	Day 1 after treatment	6-8 weeks after treatment
Basic information					
Informed consent					
Inclusion / Excluded Criteria					
Demographic information					
Vital signs					
Physical examination					
Other comorbidities					
Auxiliary check					
Blood routine					
UBT Test					
Gastroscopy					
Classify adverse events					
Diarrhea					
Stomachache					
Nausea					
Vomit					
Drug allergies					
Black stool					
Yellow urine					
Loss of appetite					

other					
Combined medication					
Random grouping					
Amount spent					

Note: Various inspections and test procedures are carried out according to the time of the research flow sheet, and occasional changes during the inspection item window period due to festivals, holidays or other management reasons are allowed; laboratory inspections are accepted within 1 week before randomization of the laboratory inspection results of our center.

[1] Physical examination: examination of the main body system (general condition, skin mucosa and lymph nodes, head, neck, chest, abdomen, genitalia, musculoskeletal, nervous system, other).

[2] Blood Routine: Red Blood Cells (RBC), White Blood Cells (WBC), Neutrophils (NEUT), Hemoglobin (HB), Platelets (PLT).

[3] Classify the incidence of adverse events: the respective incidence of each adverse event in operation, such as the incidence of sedative low blood pressure.

1 0. Management and quality control of clinical trials

10.1 Declaration

This clinical trial will be conducted in accordance with the standard operating specifications of the Third Xiangya Hospital for clinical trials and will comply with the "Declaration of Helsinki", China's GCP and clinical trial regulations. When the investigator signs the plan, he will agree to follow the instructions and procedures set out in the plan and follow the principles of clinical trial quality management practices that this plan complies with, as well as all the principles of managing local regulations and medical research.

10.2 Ethics Section

This study was designed and prepared on the basis of the Declaration of Helsinki of the World Medical Association, taking into account the rights and welfare of patients. The main investigator or investigator of the clinical trial explains to the patient the purpose of the trial and all potential possibilities. The patient voluntarily agrees to participate in the clinical trial and signs the informed consent form to become a subject. Clinical trial investigators and researchers participating in the trial should correctly analyze and be familiar with the research plan, and be able to prepare measures in advance, such as response measures in the event of unexpected adverse events, required reports, and adequate training. Clinical investigators must comply with the "Clinical Trial Quality Management Standards" when conducting clinical trial research. The main investigator and the personnel participating in the research should abide by the content specified in the test plan, and scientifically maintain the currently recognized technical level to conduct the test. According to national policies and regulations, researchers provide relevant test documents to the ethics committee. Before a clinical trial starts, the approval of the ethics committee must be obtained. The modification of the research protocol needs to be submitted to the ethics committee for approval. In the process of clinical research, if any serious adverse event or unexpected adverse event related to the safety of clinical research occurs, which may affect the safety of the patient and the implementation of the trial, the investigator must inform the ethics committee. The investigator is responsible for explaining to each subject the

purpose, methods, benefits and potential risks of this clinical trial, alternative treatment methods, and the rights and obligations of subjects in accordance with the Declaration of Helsinki; Subjects should be informed that they have the right to withdraw from the trial at any time, and their personal interests will not be harmed. Before any operational procedures related to clinical trials, an informed consent form signed by the subject must be obtained. Oral explanations must be made when giving written informed consent to subjects. The informed consent must be dated and signed by each subject or their legal guardian or agent. The signed informed consent form and information page shall be kept by the subject, and another signed informed consent form shall be kept and kept as a research file. Before any research-related process starts, the consent form must be approved and signed by the subject. Before any research-related process begins, the consent form must be approved and signed by the subject. Before obtaining informed consent, the investigator or its designated personnel shall provide the subject with sufficient time and opportunity to inquire about the details of the trial and decide whether to participate in the trial. The informed consent process needs to be recorded in the disease course record on the day of the screening visit. The investigator is responsible for the informed consent process. If any information related to the subject's willingness to continue participating in the trial is obtained during the trial, the written informed consent must be updated, and the subject must be given to confirm whether the subject is willing to continue participating. The revised informed consent form needs to be ethically approved before being provided to the subjects. By signing the informed consent form, the subject/patient will agree to allow the hospital and the health administrative department to verify the original data about the clinical research that has been obtained, and the reviewer must abide by the confidentiality statement.

10.3 Quality assurance and audit

All drugs and materials used in clinical research must be based on quality control. The hospital's clinical trial research center, scientific research department and other management departments and related medical management institutions have the right to review clinical research, the purpose of which is to ensure the authenticity of clinical research record data and comply with the provisions of the clinical research plan. When necessary, the researcher

will invite people outside the project team to conduct third-party audits, allowing the auditors to directly access the original data/documents, including all medical records, research-related documents and letters, and the informed consent documents for the clinical trial Wait. Subjects of clinical research will be informed of the review process of clinical research, but the subject's privacy and data will be strictly protected.

10.4 Medical Records Report Form

In clinical research, the CRF should be completed in time after each visit to record the condition of the subject. The medical history records and other records related to the subject's disease progression during the study are kept by the investigator. These records should include the following as much as possible: original or photocopy of laboratory data and other medical test results, which must be kept in the center together with the subjects' medical records.

10.5 Intellectual Property

All information obtained from the experiment belongs to the intellectual property rights of the Third Xiangya Hospital and the researcher team. Therefore, clinical trial investigators and all other relevant personnel must strictly keep confidential, and shall not disclose to third parties without the prior consent of the main investigator of the trial.

10.6 Subject Privacy

Researchers must ensure that the privacy of clinical trial subjects is maintained. In all public documents outside the hospital, only the screening number and initials of the clinical trial can be used to determine the identity of the clinical trial subject, but the subject's name cannot be indicated. Researchers must properly keep the names and addresses of relevant clinical trial subjects and the enrollment form corresponding to the clinical trial number. These entry forms are kept strictly confidential by the investigator and cannot be submitted to a third party.

11. Papers published

The Third Xiangya Hospital, as the sponsor, has exclusive rights to this research. Regarding the manuscript and publication, the Third Xiangya Hospital and the main researchers have the final decision.

12. Data preservation

The investigator is responsible for keeping the following data for at least 5 years after the end of the trial, and can be extended if necessary: the data obtained in the trial; the trial protocol; the original research data; the case report form; the original or photocopy of the informed consent form; the ethics committee approval, etc.

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Informed consent

Project name	Comparison of Vonoprazan fumarate-based Triple Therapy Versus Proton Pump Inhibitor and Bismuth Based Quadruple Therapy in the Eradication of Helicobacter Pylori: A Single-center Prospective Open-label Controlled Study
Clinical research unit	Third Xiangya Hospital, Central South University
Main researcher	Anliu Tang
Sponsor	Department of Gastroenterology, Third Xiangya Hospital, Central South University
Funding source	No
Informed Consent Version	1.1
Informed Consent Version Date	2021-5-22

We sincerely invite you to participate in a clinical study comparing Helicobacter pylori eradication programs. Your participation in this study is completely voluntary and you can choose not to participate. If you decide not to participate, this will not affect the relationship between you and the doctor. In order for you to decide whether or not to participate in this study, it is important to understand the content of the study in detail. Please read the following information carefully, and you can also discuss it with your family, friends, and doctor. If you don't understand anything or want to learn more about this study, please feel free to ask your doctor.

1.Test drug

The triple therapy and quadruple therapy in this project are composed of two types of drugs, basic experimental drugs and antibiotics, and a total of 4 treatment options. The treatment plan of triple therapy is: vonoprazan fumarate + amoxicillin + doxycycline, vonoprazan fumarate + furazolidone + doxycycline. The treatment plan of quadruple therapy is esomeprazole + colloidal bismuth tartrate + amoxicillin + doxycycline, and esomeprazole + colloidal bismuth tartrate + furazolidone + doxycycline.

The basic test drug for triple therapy is vonoprazan fumarate, a drug produced by Tianjin Takeda Company, which is a powerful drug that inhibits gastric acid secretion, mainly by blocking the K + channel of H + , K + -ATPase , Competitively blocking the binding of K + with the enzyme, can stay in the parietal cells for a long time, thereby quickly inhibiting the secretion of gastric acid. Although the current indication for the vonoprazan fumarate produced by Tianjin Takeda is to treat reflux esophagitis, the drug has been approved by the U.S. Food and Drug Administration (FDA) and believes that it can cure Helicobacter pylori together with antibiotics. , China’s Fifth National Consensus Report on the Treatment of Helicobacter Pylori Infection" mentioned that the use of this drug can increase the cure rate of Helicobacter pylori. In addition, the treatment plan of the drug combined with antibiotics has been confirmed in several studies in Japan due to the traditional quadruple therapy.

The basic test drugs for quadruple therapy are esomeprazole and colloidal bismuth tartrate capsules, produced by AstraZeneca Co., Ltd., and Shanxi Xinbaoyuan Company, respectively; among them, esomeprazole is a proton pump inhibitor. It can inhibit the secretion of gastric acid and is a commonly used acid suppressing drug in clinical practice; colloidal bismuth tartrate capsule is a commonly used gastric mucosal protective drug. After oral administration, a colloidal sol with excellent colloidal properties is formed in the gastric juice to form a protective film to isolate gastric acid.

There are two combinations of antibiotics for triple therapy and quadruple therapy: amoxicillin + doxycycline and furazolidone + doxycycline. Amoxicillin is produced by Hainan General Sanyo Pharmaceutical Co., Ltd., and is one of the most used semi-synthetic penicillin broad-spectrum β-lactam antibiotics. Furazolidone is produced by Tianjin Lisheng Company and is a nitrofuran antibiotic. Doxycycline is produced by Jiangsu Yongxin Company and is clinically classified as a tetracycline antibiotic. It is mentioned in the "Fifth National Consensus Report on the Treatment of Helicobacter Pylori Infection in China" that the resistance rate of Helicobacter pylori in China to these three antibiotics is very low.

Currently, there are other treatment options for Helicobacter pylori, including sequential therapy. If you do not want to participate in this study, you can use this program to eradicate Helicobacter pylori.

2. Research purpose and basic research content

Helicobacter pylori (Hp) infection is one of the most common chronic infections in humans. China is one of the countries with a high incidence of Hp infection. Epidemiological surveys show that the current Hp infection rate in China is 42% -64% . Hp infection is closely related to the occurrence of chronic active gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer.

There are many different therapies for the treatment of Hp . In China, bismuth-containing quadruple therapy is highly recommended as the first-line treatment for Hp infection. Although the eradication rate has increased, the therapy still has

limitations, including bismuth-related side effects, poor patient compliance with medications, high resistance rates to clarithromycin and metronidazole, and high drug costs. In recent years, a new acid-suppressing drug-potassium ion competitive acid blocker has been introduced. Its novel mechanism of action and unique pharmacokinetic characteristics make it show better characteristics than PPI, such as fast onset, The structure is stable, the acid suppression effect is long-lasting, the individual differences are small, and the adverse reactions are few. As its representative medicine, vonoprazan fumarate green tablets are mainly used to treat acid-related diseases, including reflux esophagitis, gastric ulcer, and duodenal ulcer. A number of clinical studies have shown that vonoprazan fumarate raw tablets are safe, effective and well tolerated in the treatment of reflux esophagitis and eradication of Hp. Considering the high drug resistance rate of clarithromycin and the huge side effects caused by the large dose of amoxicillin in dual therapy, we are trying to find a better alternative therapy based on vonoprazan fumarate green tablets, which can as a first-line solution for Hp eradication.

Four treatment options were selected in this study: triple therapy based on vonoprazan fumarate + amoxicillin + doxycycline, vonoprazan fumarate + furazolidone + doxycycline, and quadruple therapy based on PPI and colloidal bismuth tartrate capsules-esomeprazole + colloidal bismuth tartrate capsules + amoxicillin + doxycycline, esomelar Azole + colloidal bismuth tartrate capsules + furazolidone + doxycycline. Considering the main result, the objectivity of the detection of Hp eradication rate, the open-label design is unlikely to bias the results. We carry out a single-center, prospective, open-label clinical controlled study for the eradication of Hp infection to evaluate the effectiveness of the four treatment options, the incidence of adverse events, patient compliance and economic benefits. Trying to determine whether triple therapy based on vonoprazan fumarate can be used as a first-line treatment to eradicate Hp in Chinese patients , thereby improving clinical outcomes, improving patient compliance, avoiding unnecessary side effects, and reducing the incidence of Hp infection the cost of.

Entry criteria：

6. 年龄≥18 岁，≤80 岁

7. Age ≥18 years old, ≤80 years old；

8. Urea breath test (UBT) is positive for Hp infection

9. Receive gastroscopy within 1 month

10. Clearly understand, participate in the research voluntarily, and sign the informed consent form

11. Anti-Hp treatment without any treatmentform

Includsion criteria：

Subjects who meet any of the following criteria cannot be selected for this trial:

：

Firstly, the patient's physical condition is unable to receive Helicobacter pylori radical treatment ：

7. Allergic to the drugs used in this clinical study；

8. Use PPI, histamine H2 receptor antagonist, antibiotics, bismuth, probiotics or drugs with antibacterial effect within 4 weeks before study treatment；

9. Use adrenal corticosteroids, non-steroidal anti-inflammatory drugs and anticoagulants;

10. There are diseases or clinical conditions that may interfere with the evaluation of research and treatment, such as liver disease, cardiovascular disease, lung disease, kidney disease, metabolic disease, mental disease or malignant tumor;

11. Pregnant or breastfeeding women;

12. Participate in other clinical studies within 3 months before the registration of this clinical study;；

Secondly, Disagree to participate in this research.

Thirdly, There are other problems that do not meet the requirements of this research or that affect the results of the research：

1. Suspected history of antibiotic abuse

2. Patients with craniocerebral injury, mental illness or epilepsy, etc. unable to communicate with patients or other diseases that may affect follow-up：

If the subject meets any of the following criteria, the researcher will suspend the study early:

1. Allergic reactions to the drugs or other components used in this clinical trial
2. In the event of an adverse event, the investigator judges that the study needs to be terminated early, because continuing to participate in the study may bring unacceptable risks to the health of the subject, or the subject is unwilling to continue participating in the study due to adverse events

Exit criteria：

If the subject meets any of the following criteria, the patient will withdraw from the study：

1. Subject withdrew informed consent
2. Subject was lost to follow-up.

The project has been approved by the ethics committee of Third Xiangya Hospital of Central South University. This study was conducted at the Third Xiangya Hospital of Central South University. A total of about 596 patients infected with Helicobacter pylori participated in this study. The study time limit is 2021.06.15-2022.06.15, and all participating patients have a one-quarter chance of being randomly assigned to the four schemes (Table 1).

Table 1 The specific medications of the four groups of patients

	Group1	Group2	Group3	Group4
Esomeprazole (5mg, 2 times /d, orally half an hour before meals)	√	√		
Colloidal bismuth tartrate (220mg, 2 times /d, orally half an hour before meals)	√	√		
Amoxicillin (1000mg, 2 times /d, orally after meals)	√		√	
Furazolidone (100mg, 2 times /d, orally after meals)		√		√
Doxycycline (100mg, 2 times /d, orally after meals)	√	√	√	√
vonoprazan fumarate (20 mg, 2 times /d).			√	√

If you choose not to participate in this study, it will not affect your current and

future treatment at all. You can use other radical treatment options, such as sequential therapy.

3. Research process and methods

This research is roughly divided into the following steps:

a) Informed Consent and Patient Screening

b) Collect patient-related information

c) Random grouping

d) Eradication therapy

e) Patient follow-up

f) Remedial measures for failure to eradicate and adverse reactions

g) Result evaluation index collection, including eradication, drug compliance, incidence of adverse events, drug costs

h) Statistical Analysis

The duration of this study is roughly: the screening period is 7 days, the treatment period is 14 days, and the follow-up period is 4-8 weeks. During the entire study period, you need to visit the hospital 3 times during the screening period and the follow-up period. During the study period, you will have multiple or one of the blood routine, UBT examination, gastroscopy, and questionnaire survey. The specific frequency of each examination will be determined by the doctor according to the development of your condition. The total expected cost is not much different from the normal Hp eradication program.

4-6 weeks after the end of the eradication treatment, a UBT test was performed to determine whether Hp was eradicated. During this period, no antibacterial drugs, bismuth, or PPI were taken. Use ITT analysis and PP analysis.

The first visit is the screening period. Your eligibility will be screened. If you meet all the selection criteria, you will participate in this study. The contents of the examination are as follows: medical history collection and physical examination: examination of the main body systems (general conditions, skin, mucous membranes and lymph nodes, head, neck, chest, abdomen, anogenitals, musculoskeletal, nervous system, etc.); blood; UBT Check: to determine whether you have Hp

infection; gastroscopy.

The second visit is the first day after the end of treatment, and it lasts for one day. You will have the following examinations or inquiries: physical examination, MMAS questionnaire, occurrence of adverse events, and drug costs.

The third visit is 4-8 weeks after the end of treatment, and lasts for 1 day. You will have the following examinations: physical examination, UBT test.

4. Possible risks and inconveniences

All drugs usually have side effects, and no matter which treatment you take, there will be other risks. We list the possible adverse reactions and precautions of each drug in accordance with the latest version of the drug instructions (Table 2). In addition, we have listed all other drugs that may interact with the study drug (Table 3). During the treatment period, we hope that you should disable or use other drugs with caution. If you have any discomfort, please tell your doctor in time.

Table 2 Possible adverse reactions and precautions of study medication

	adverse reactions	**Precautions**
Essomelazole	Whole body: abdominal swelling, allergic reactions, fatigue, back pain, chest pain, pain under the breastbone, facial edema, peripheral edema, hot flashes, fatigue, fever, flu-like symptoms, generalized edema, leg edema, discomfort, pain, chills: Cardiovascular: flushing, hypertension, tachycardia. Endocrine: Goiter. Gastrointestinal tract: abnormal bowel function, constipation, dyspepsia, dysphagia, gastrointestinal dysplasia, upper abdominal pain, belching, esophageal disease, frequent stools, gastroenteritis, gastrointestinal bleeding, gastrointestinal symptoms (non-specific), hiccups, melena, oral disease, pharyngopathy, rectal disease, increased serum gastrin, tongue disease, tongue edema, ulcerative stomatitis, vomiting, gastrointestinal candidiasis, clostridium difficile Diarrhea, pancreatitis, bilirubinemia, abnormal liver function; Hearing: earache, tinnitus.	Prohibited for drug allergies The lowest dose and shortest course of treatment suitable for the treatment situation. It may increase the risk of fractures of the hip, wrist or spine caused by osteoporosis. It is expected that PPI therapy needs to be extended or combined with drugs such as digoxin or drugs that can cause magnesemia (eg, diuretics). Medical professionals may consider monitoring the blood magnesium concentration before starting PPI therapy and regularly. Accompanied by rare genetic diseases, patients with glucose intolerance, glucose-galactose malabsorption, or

	Immune system: immediate allergic reaction/shock. blood system: anemia, hemoglobin reduction anemia, cervical lymphadenopathy, snoring, leukocytosis, leukopenia, thrombocytopenia. Metabolism/Nutrition: Diabetes, hyperuricemia, hyponatremia, elevated alkaline phosphatase, thirst, vitamin B12 deficiency, weight change. Musculoskeletal system: joint pain, worsening arthritis, arthropathy, cramps, anal pruritus, skin rash, erythema, maculopapular rash, skin inflammation, increased sweating, urticaria. Feelings: otitis media, perverted sense of smell, loss of taste, perverted sense of taste, blurred vision, Urogenital system: abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, frequent urination, candidiasis, genital candidiasis, polyuria.	sucrase-isomaltase deficiency should not take this product Patients who have been treated with the drug for a long time (especially those treated for more than 1 year) should be monitored regularly. There may be a decrease in the absorption of vitamin B12 due to decreased penicillin or skin deficiency. Therefore, in long-term treatment, for patients with reduced body expansion or risk factors for reduced vitamin B12 absorption, this risk needs to be considered.
Colloidal tartare	The mouth may smell of ammonia, the tongue coating and stool are gray-black, nausea, and constipation	Drug allergies are forbidden; cannot be taken with milk and antacids at the same time
Amoxicillin	Diarrhea, indigestion, nausea, vomiting, urticaria and erythema	Drug allergies are forbidden; those with liver and kidney dysfunction/creatinine clearance less than 30 ml/min should be used with caution; those with anticoagulants should be used with caution.
Furazolidone	Nausea, vomiting, diarrhea, headache, dizziness, drug-heat rash, anal itching, asthma, orthostatic hypotension, hypoglycemia, lung infiltration, hemolytic anemia, jaundice, polyneuritis	Disabled for drug allergies; disabled for glucose-6-phosphate dehydrogenase deficiency; forbidden to drink alcohol; not suitable for patients with ulcer disease or bronchial asthma
Doxycycline	Nausea, vomiting, abdominal pain, diarrhea, liver toxicity, pancreatitis, allergic reactions (macro papules and erythema, urticaria, angioedema, allergic purpura, pericarditis and systemic lupus erythematosus skin lesions, exfoliative dermatitis, Anaphylactic shock and asthma) blood system (hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia); central nervous system (headache, vomiting, optic nerve head edema) double infection; reduction of normal flora in the body , Vitamin deficiency, fungal reproduction (dry mouth, pharyngitis, angular cheilitis and glossitis)	The drug is disabled for allergies
Vonoprazan fumarate	Diarrhea, constipation, nausea, and bloating. Headache, rash, edema, eosinophilia, liver toxicity, jaundice, skin, and subcutaneous diseases such as erythema multiforme	Drug allergies are prohibited; patients who are receiving atazanavir or rilpivirin are contraindicated

Table 3: Study the combined drug interactions of drugs

	Drug/food interactions
Esomeprazole	Omeprazole (esomeprazole is its enantiomer) can interact with some reversal antiviral drugs (atazanavir, nelfinavir), so combined therapy is not recommended. It can inhibit gastric acid secretion. Therefore, for drugs whose bioavailability is greatly affected by gastric pH (such as ketoconazole, itraconazole, atazanavir, iron salts and digoxin), esomeprazole Can affect its absorption. Be cautious or prohibit other drugs related to the metabolism of CYP2C19 and CYP3A4 (such as diazepam, citalopram, imipramine, clomipramine, phenytoin, voriconazole, cilostazol, rifampin, Hypericum perforatum, etc.). Co-administration with tacrolimus can lead to an increase in the blood concentration of tacrolimus. The decrease in gastric acid caused by the drug can lead to the proliferation of intestinal chromaffin-like cells and the increase of chromogranin A levels, thus interfering with the examination of neuroendocrine tumors. Combined use with methotrexate may increase the serum concentration of methotrexate and/or its metabolites.
Colloidal bismuth tartrate	Milk and antacids can interfere with the effect of this product and should not be taken at the same time. Taking tetracycline together will affect the absorption of the latter. If it is used at the same time with other drugs, drug interactions may occur. For details, please consult your physician or pharmacist.
Amoxicillin	This product may reduce the effect of oral contraceptives; it is not recommended to use probenecid or allopurinol in combination.
Furazolidone	Combination with tricyclic antidepressants can cause acute toxic psychosis and should be avoided. Can enhance the effect of levodopa. Sympathomimetic amines, foods rich in tyramine, appetite suppressants, monoamine oxidase inhibitors, etc. can enhance the effect of this product.
Doxycycline	This product can inhibit the activity of plasma prothrombin, so patients receiving anticoagulant therapy need to adjust the dose of anticoagulant. When barbiturates, phenytoin or carbamazepine are used together with this product, the above-mentioned drugs can reduce the blood concentration of doxycycline due to the induction of microsomal enzyme activity, so the dose of doxycycline must be adjusted.
Vonoprazan fumarate	Should not be taken with atazanavir or rilpivirin, be cautious with nelfinavir, itraconazole, tyrosine kinase inhibitors (gefitinib, nilotinib, erlotinib), Take caution with digoxin and methyldigoxin, and take caution with CYP3A4 inhibitor clarithromycin

The adverse reactions and risks that you may have during the study period include but are not limited to the above. Any study drug may have other unforeseen or even serious adverse reactions. If new adverse reaction information is discovered during the period, the research doctor will also inform you in time. At the same time, the study doctor will closely observe your condition and determine whether you

have had an adverse reaction, and if necessary, other drugs will be used to treat you to reduce the adverse reaction or discomfort.

If you are breastfeeding or pregnant, you will not be able to participate in this project.

5. Expected benefits

Using the new drugs in this study and strict follow-up, you may get a safer treatment process and better medication experience; in addition, you will receive follow-up follow-up 1 day, 4-8 weeks after treatment, and the eradication Patients who fail and have adverse reactions actively undergo relevant evaluation and treatment, which helps to ensure the safety of your treatment. In general, you will receive stricter clinical monitoring during the study period and will be able to discuss your treatment with the study doctor.

Due to individual differences, we cannot predict whether different medication regimens will have side effects on you, and the size of the side effects, so you may not benefit from this clinical trial. If you do not want to participate in the project, use our hospital's conventional Hp eradication treatment plan. This program is relatively widely used and has good safety, but there are still a series of side effects.

The free check you need to complete during the trial is as follows: MMAS score.

6. Compensation and treatment

When you have a serious adverse reaction during treatment, the trial will be terminated immediately, and we will take all necessary measures to rescue you. If you find that the radical cure is not successful at the second follow-up visit, you will receive a treatment that is different from the previous radical cure plan and follow up again after taking the medicine for 14 days and one month after stopping the medicine. If the second radical cure fails, the drug will be discontinued for half a year, and after half a year, the patient will receive a different treatment from the previous two radical cures.

This study will not increase your treatment risks, inspection costs, and treatment costs. In addition, you need to undergo follow-up and evaluation within 1-3 days and 4-8 weeks after treatment, each time it may take 10-20 minutes. If you

experience any discomfort, new changes in your condition, or any unexpected situation during this study, regardless of whether it is related to the operation, please inform your study doctor in time, and they will make serious judgments and rigorous medical treatment. deal with.

When the test-related damage occurs to the subject, the sponsor shall bear all the costs of the treatment and the corresponding economic compensation or compensation. The specific amount of compensation will be determined by the results of the appraisal of the relevant department and the negotiation between the two parties (the subject and the hospital).

7. Privacy and confidentiality

Your medical information will be kept confidential at all times. In addition to your research doctor, the sponsors, monitors, auditors, ethics committees, and health supervision departments of this research may consult your original medical data related to the research to ensure that the research is standardized and the data is true and reliable . However, all information will be kept confidential, and the results of this study may be published in medical journals, but your identity will not be revealed.

8. Precautions for subjects before, after and during the research process

Before participating in this research, please read carefully the selection criteria and exclusion criteria of the study, and make sure that you meet the selection criteria and there are no problems mentioned in the exclusion criteria; during the research process, if you have any physical discomfort, please Inform your doctor, and the doctor will deal with your situation accordingly; when you need to follow-up, please cooperate with the follow-up doctor as much as possible to make a more accurate and timely diagnosis, which is beneficial to your treatment; finally, you are studying During the process, if you have any questions about this study, you can contact your research doctor, who will answer you in detail.

There are a variety of solutions to cure H. pylori. If you encounter the following situations and need to terminate the clinical trial, you will continue to receive the

hospital's conventional treatment plan or other alternatives under the supervision of the clinician.

The following are the circumstances and reasons that the project may be terminated:

When the subject has more serious adverse reactions, such as anaphylactic shock, severe liver and kidney damage, the test will be terminated immediately and all necessary measures will be taken for rescue.

9. Your rights

If you are unwilling to participate in the project, use our hospital's conventional Hp eradication treatment plan, including but not limited to sequential plan, or other bismuth-containing quadruple radical treatment plan. This will not affect your Hp eradication process.

If there is any important new information about the study drug during the study period that may affect your willingness to continue participating in the study, we will notify you and discuss with you whether you should continue the study.

You can request to withdraw from this study at any time for any reason. To ensure your safety, please complete the last visit so that the doctor can complete all the inspection items required by the last inspection and discover possible adverse reactions. Whether you participate or refuse to participate in this study, or withdraw from the study halfway, you will not be discriminated against or retaliated, and your medical treatment and rights will not be affected.

If the informed consent form is updated during the research process, you will need to sign the new version of the informed consent form again. After the study is over, if you need specific information about medication, you can consult your study doctor.

During the research process, we will provide you with a comprehensive evaluation of relevant indicators (screening period), drug use monitoring (treatment period), and evaluate whether Hp is eradicated (follow-up period); after the study, if you still have Medical questions related to this project need to be consulted. After contacting your research doctor, we will try our best to answer you.

10. Special protection for vulnerable subjects

Vulnerable subjects refer to subjects who are insufficient or have lost the ability to maintain their own wishes and rights, whose willingness to participate in clinical trials voluntarily, may be expected to benefit from the trial, or who refuse to participate may be improperly affected by retaliation. Including: the researcher's students and subordinates, the sponsor's staff, military personnel, prisoners, patients with incurable diseases, patients in critical situations, people staying in orphanages, homeless persons, persons with no capacity for civil conduct, or restricted civil conduct Ability people and so on.

Special protective measures: The above-mentioned patients will be excluded from the subjects.

11. Collection, preservation, utilization and external provision of biological specimens (if involved)

The blood samples collected during the research process will be collected in the fifth examination and sent by the research doctor to the laboratory of our hospital for processing. There is no need to leave the country, and no genetic information is involved.

12. Contact information

If you have any concerns or questions about the study, or in any emergency, please contact your doctor in time. Please keep this information.

Doctor's name：_____

Contact number：_____

If you have any questions about your rights, you can contact:

Ethics Committee of the Third Xiangya Hospital of Central South University

Contact number: 0731-88618938

Consent statement

I have read the above content and understand the nature and purpose of the study, and the possible adverse effects of the drug, and I could discuss and ask questions about this study with the doctor. All the questions I raised have been answered satisfactorily.

I agree to visit the doctor on time during the study, and accept the corresponding examinations related to this study. I will abide by the instructions and requirements of the subjects, and fully cooperate with the researchers, truthfully and objectively provide the researchers with the health status and related information before participating in the study, during the study and during each follow-up period.

I understand that participation in the study is voluntary. I confirm that I have sufficient time to consider this, and I understand that I can withdraw from the study at any time, and my subsequent treatment will not be adversely affected by this. I understand that the doctor has the right to be at any time based on my situation. Discontinue the study.

I hereby express my consent to participate in this clinical study, and I will obtain a signed and dated copy of the informed consent form._

Subject's name : Tel: _____

Subjects Signature: Date: _____ Year _____ month _____ day

(If involved) Guardian (relationship): Tel: _____

Check Name: Date: _____ Year _____ month _____ day

(If involved) Name of fair witness: Tel: _____

Check Name: Date: _____ Year _____ month _____ day

I have explained the relevant details of the study to the above-mentioned subjects who participated in the study, and provided the subjects with a signed informed consent form.

Researcher's name :

Tel：_____

Researchers Signature :

Date：_____