BMJ Open

Efficacy of quadruple regimen with polaprezinc for gastric *Helicobacter pylori* infection eradication: protocol for a single-centre, single-blind, non-inferiority, randomised clinical trial

Dingkun Wu ,[1,2] Zhen Sun,[3] Tingyuan Li,[2] Qinwen Tan,[2,4] Yue Sun,[2] Tingting Chen,[5] Yujing Liu,[6] Jun Li,[7] Haidong Jiang,[7] Zhiqiang Yuan,[7] Yuqian Zhao ,[2] Wen Chen[2,6]

To cite: Wu D, Sun Z, Li T, *et al*. Efficacy of quadruple regimen with polaprezinc for gastric *Helicobacter pylori* infection eradication: protocol for a single-centre, single-blind, non-inferiority, randomised clinical trial. *BMJ Open* 2020;**10**:e037182. doi:10.1136/bmjopen-2020-037182

► Prepublication history and additional material for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-037182).

Received 22 January 2020
Revised 11 September 2020
Accepted 22 September 2020

For numbered affiliations see end of article.

Correspondence to
Dr Yuqian Zhao; gw_zhaoyuqian@126.com and Dr Wen Chen; chenwen@cicams.ac.cn

ABSTRACT

Introduction *Helicobacter pylori (H. pylori)* is the most well-known risk factor for gastric cancer. At present, *H. pylori* shows varying levels of resistance to different treatments, leading to a lower rate of *H. pylori* eradication. The aim of this study is to evaluate the efficacy of polaprezinc-containing quadruple therapy (PQT) for the eradication of *H. pylori* infection and, thus, to provide more evidence to inform the clinical treatment of *H. pylori* infection in China.

Methods and analysis This is a single-centre, single-blind, non-inferiority, randomised controlled trial, enrolling 158 patients with *H. pylori* infection. Patients are randomised (1:1) to the two groups for a 14-day therapy. Treatment group: PQT (esomeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg, polaprezinc 75 mg) two times per day; control group: bismuth-containing quadruple therapy (esomeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg, bismuth potassium citrate 220 mg) two times per day. The primary outcome is the rate of *H. pylori* eradication. Secondary outcomes are the incidence of adverse events and the gastrointestinal microbiota distribution. The 16S ribosomal RNA (16S rRNA) next-generation sequencing (NGS) is used to evaluate the effect of two different therapies on the distribution of the gastrointestinal microbiota.

Ethics and dissemination This study was approved by the Ethics Committee of Sichuan Cancer Center & Hospital (No. SCCHEC-02-2019-015). Any amendment to the research protocol will be submitted for ethical approval. All participants must provide informed consent. On completion, the results of the study will be published in the appropriate peer-reviewed journal.

Trial registration number ChiCTR1900025800; preresults.

Strengths and limitations of this study

- The study design (randomised controlled trial, RCT) is the gold standard of clinical evidence.
- This is the first RCT to compare the efficacy of polaprezinc-containing quadruple therapy and bismuth-containing quadruple therapy on *H. pylori* eradication.
- The results of this study could provide more evidence to inform the clinical treatment of *H. pylori* infection in China.
- This is the first prospective study with next-generation sequence detecting strategy in Chinese mainland to explore the possible drug-resistance mechanism of *H. pylori*.
- The single-centre clinical trial may not represent the *H. pylori* eradication rate of general population.

INTRODUCTION

Helicobacter pylori (H. Pylori) is a multiflagellum, microaerobic Gram-negative, bacillus, that is specifically colonised in the gastric epithelium.[1] It is estimated that about 50% of the world's population is infected with *H. pylori*,[2 3] but the infection rate for *H. pylori* varies widely by population, age, geographic region, race, socioeconomic status, health status, population density and eating habits.[2 3] *H. pylori* is one of the most important pathogenic factors of gastrointestinal diseases such as chronic gastritis, peptic ulcer, gastric adenocarcinoma and gastric mucosa - associated lymphoid tissue (MALT) lymphoma.[4 5] Moreover, *H. pylori* infection is correlated with a 1-fold to 10-fold increase in the risk of gastric or duodenal ulcer and with 0.1%–3% risk of developing gastric cancer.[6] The eradication of *H. pylori* is an important method for the treatment of digestive tract ulceration and chronic gastritis and for the prevention of gastric cancer.

At present, a combination of therapy is recommended for the treatment of *H. pylori* infection in clinical practice as well as for the

treatment of gastritis and digestive ulcer caused by *H. pylori* infection. Among available treatments, the use of bismuth, in combination with antibiotics, such as metronidazole, amoxicillin, clarithromycin, azithromycin, levofloxacin, chloramphenicol and tetracycline, has been widely recommended. Polaprezinc, a chelating agent of L-carnosine and zinc, can block the colonisation of *H. pylori* by inhibiting its activity pharmacologically and the associated inflammatory chain reaction and removing urea, enzymes, monochloramines to achieve the *H. pylori* eradication. Polaprezinc combination with lansoprazole, amoxicillin and clarithromycin can increase the *H. pylori* eradication rate from 24/31 (77.4%, triple therapy alone) to 33/35 (94.3%).[7] However, the efficacy of *H. pylori* infection treatment in high-risk population in China is needed to be established.

With the frequent use of antibiotics, the rate of antibiotic resistance also showed an upward trend. Studies reported on the resistances of *H. pylori* to various antibiotics, which lead to lower *H. pylori* eradication rates. A large number of studies outside China have been conducted to detect the drug-resistance sites of *H. pylori*, with the plausible mechanisms leading to resistance for many antibiotics having been defined.[8–12] Moreover, the use of drugs to treat *H. pylori* infection has been associated with significantly different degrees of overgrowth of the gastric microbiota.[13] Compared with patients with gastritis, the diversity of gastric microbiota among patients with gastric cancer is significantly lower, with the abundance of Helicobacter species being specifically decreased, while the abundance of other species is increased.[14] The effect of different treatment options for treatment of *H. pylori* infection on the distribution of the other microbiota in the gastrointestinal is unknown.

The 16S ribosomal RNA (16S rRNA) next-generation sequencing(NGS) technology is a powerful tool for microbial detection and classification. The 16S rRNA sequence information is obtained by comparing the gene sequences of the 16S rRNA gene fragment of various organisms, with the sequence information obtained by cloning, sequencing or enzyme cutting or probe hybridisation. The 16S rRNA sequence information is then compared with the data in the 16S rRNA database for identification and is not affected by antibiotics. It can identify dead bacteria and microorganisms that currently cannot be cultivated artificially as well as identify new types of microorganisms that play an important role in intestinal microbiota detection.[15 16]

The aim of our study is to evaluate the efficacy of polaprezinc-containing quadruple therapy (PQT) compared with the traditionally bismuth-containing quadruple therapy (BQT) for *H. pylori* eradication and, thus, to provide evidence for clinical treatment of *H. pylori* infection in Chinese population.

METHOD AND ANALYSIS

Design

This protocol is a single-centre, single-blind, non-inferiority, randomised clinical trial, in which 158 patients with *H. pylori* infection will be enrolled. Patients will be randomly assigned into one of the study groups in a 1:1 allocation ratio (figure 1). Patients are required to come to hospital on day 7 after taking drugs for receiving next-cycle drugs and follow-up the adverse events (AEs). Phone follow-up is used to monitor AEs on day 14 after taking drugs. All patients will be called back within week 4–8 after the end of therapy. This study follows the Consolidated Standards of Reporting Trials guidelines.

Measured outcomes (and associated processes) are summarised in table 1. The 16S rRNA will be performed to sequence the gastrointestinal microbiota in the collected samples.

This study will be conducted at Yanting County Cancer Hospital. It began in December 2019 and is projected to take 1 year to complete.

Objectives

The three objectives of the study are as follows. The first is to evaluate the efficacy and safety of PQT for eradication of *H. pylori* infection. The second is to detect the antibiotic drug-resistance mutation sites of *H. pylori* and explore the association between the therapy and the drug-resistance sites. The third is to compare the distribution of gastrointestinal microbiota, before and after the therapy and between the different therapies.

Inclusion criteria

The enrolled patients should be 18–65 years of age, residents who participated in early screening for upper gastrointestinal cancer and the outpatients at Yanting County Cancer Hospital, with a positive primary ^{14}C urea breath test (^{14}C-UBT) for *H. pylori* infection, with no evidence of gastric cancer or other severe gastric disease identified on gastroscopy and should provide written informed consent.

Exclusion criteria

Potential participants will be screened on the following exclusion criteria: prior antibiotics or bismuth therapy within 4 weeks of enrolment; prior proton pump inhibitor (PPI) therapy within 2 weeks of enrolment; pregnancy or lactation in women; history of cardiovascular and other severe diseases; participation in other clinical studies within 3 months; unable to follow the study procedures (eg, due to mental illness or severe neurosis); history of allergy to medications used and any contraindication to gastroscopy.

Criteria for termination in the study

The following criteria will support termination of a patient's participation in the study: deterioration of health status or severe complications; severe adverse effect on the drug used that cannot be tolerated by the patient; other conditions that would affect the measurement of the outcomes; pregnancy during the treatment and lost to follow-up.

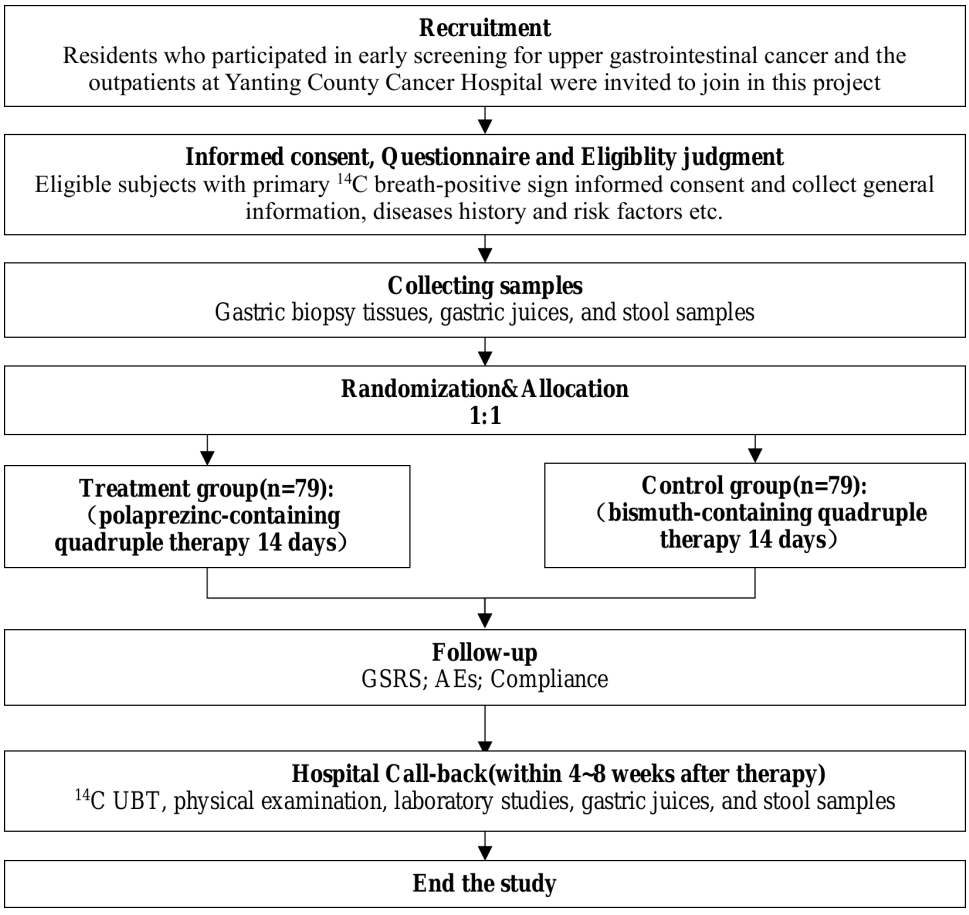

Figure 1 Flowchart of the clinical study. treatment group: esomeprazole, amoxicillin, clarithromycin and polaprezinc. Control group: esomeprazole, amoxicillin, clarithromycin and bismuth potassium citrate. ^{14}C UBT, ^{14}C-urea breath test; AEs, adverse eventsGSRS, gastrointestinal symptom rating scale.

Allocation and blinding

Patients will be randomly allocated to the two groups of the study, namely, the treatment group (PQT) and the control group (BQT), by an independent researcher using a computer-generated random sequence, with a 1:1 allocation ratio. The drugs are packaged in identical boxes, ensuring that the drugs cannot be identified on packaging appearance. The drugs are controlled by an independent drug administrator and the doctor assigned the drugs to the participants strictly according to the protocol. All patients in the study will be blinded to the assignment.

Interventions

All enrolled patients will complete physical examination and laboratory tests, including complete blood count, blood chemistry and urine tests, electrocardiogram (ECG) and gastroscope. Stools, gastric juices and biopsy tissues will be collected before therapy. Patients with a confirmed *H. pylori* infection, who meet the inclusion criteria, will be randomly assigned to the two groups of the study. As per the sample size calculation described below, 79 patients will be enrolled into each group. Patients in the treatment group will receive a 14-day PQT (esomeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg, polaprezinc 75 mg) two times per day. Patients in the control group will receive a 14-day BQT (esomeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg, bismuth potassium citrate 220 mg) two times per day.

Outcomes

The primary outcome of this study is the rate of *H. pylori* eradication, 4 weeks after the end of therapy, as measured by a ^{14}C-UBT. The secondary outcomes are the incidence of AEs and the gastrointestinal microbiota distribution before and after the therapy and between the different therapies.

Table 1 Project flow and follow-up items.

	Before treatment/ baseline	Period of treatment/intervention and follow-up (14 days)		After the treatment/ call-back
Project	0 week (–5 to –1 days)	1 week/day 7	2 weeks/day 14	Within 4–8 weeks
Screening	×			
Informed consent	×			
Inclusion and exclusion criteria	×			
Medical history collection	×			
Vital signs	×	×	×	×
Randomisation	×			
Blood routine test	×			×
Urine routine test	×			×
Renal function test	×			×
liver function test	×			×
ECG	×			×
^{14}C UBT	×			×
Stool *H. pylori* antigen	×			×
Specimens	×			×
Treatment and follow-up		×	×	×
Concomitant medications	×	×	×	×
AEs		×	×	×
Surplus medicines recycling			×	

The '×' is the item or operation content that must be performed in the project.
^{14}C UBT, ^{14}C-urea breath test; AEs, adverse events.

Follow-up

Self-reported severity of gastrointestinal symptoms is assessed on day 7 and 14 after taking drugs. The Gastrointestinal Symptom Rating Scale (GSRS) has 15 items included in five symptom clusters depicting reflux, abdominal pain, indigestion, diarrhoea and constipation, its symptoms are graded on a 7-point Likert scale (1 means absence of symptoms, 7 means with much trouble symptoms). The GSRS was found to be good, with acceptable reliability and validity.[17] Self-reported symptom severity is obtained by patient interviews on day 7 and day 14 after taking drugs. Patients are required to come to hospital on day 7 after taking drugs for receiving next-cycle drugs and follow-up the AEs. Phone follow-up is used to monitor AEs on day 14 after taking drugs. All AEs and serious AEs are recorded and will be submitted to the Medical Ethics Committee of Sichuan Cancer Center & Hospital(SCC).

^{14}C-UBT is carried out for confirmation of *H. pylori* eradication.[18] Physical examination and laboratory studies (including complete blood count, blood chemistries, urine test, ECG and gastroscopy) will be repeated 4–8 weeks after the end of therapy. Meanwhile, stools, gastric juices will be collected.

Sample size estimation

As appropriate for a non-inferiority study, the calculation of the sample size was based on the primary outcome, the eradication rate of *H. pylori*. A previous single-centre, small sample size study conducted in Japan determined that polaprezinc combined with triple therapy increased the *H. pylori* eradication rate from 77.4% to 94.3%.[7] Another randomised, open-label, non-inferiority, phase 3 study reported an *H. pylori* eradication rate of 80% when treated using bismuth subcitrate potassium, metronidazole and tetracycline, in combination with omeprazole, as a quadruple therapy.[19] Based on these data, we calculated that 63 participants were required in each group for a one-sided α value of 0.025 and power of 80%. A high proportion is better, control group proportion of 80% and the non-inferiority margin of −20% are set to identify group difference in the rate of *H. pylori* eradication. Considering a drop out rate of 20%, a sample of 79 patients in each group is required. The sample size analysis was performed using PASS (V.15.0; NCSS, LLC, USA).

Patient and public involvement

No patients or members of the public participated in the conception of our study. On completion, however, the results of the study will be published in the appropriate journal.

Data collection and management

A project-specific data entry group will be established at SCC before the initiation of the study. Two individuals are responsible for the data entry and double check the accuracy of the data entered. Data will be entered in

an encrypted ACCESS database, developed by the data administrator at SCC, who is responsible for monitoring the data.

Access to the original case report form (CRF) and database is restricted to the data entry personnel, investigators and other relevant researchers authorised by the principal investigator.

Data analysis

All statistical analyses are performed by the statistician at SCC using SPSS (V.17.0; SPSS, Chicago, Illinois, USA). Intention-to-treat (ITT) and per-protocol (PP) analyses are used to evaluate the primary outcome of *H. pylori* eradication. The ITT population included patients who meet the criteria, randomised, take at least one dose of drugs after enrolled. Missing observations are accounted for using the predictive mean matching (PMM) method. The PP population included patients who complete the designated therapy of this protocol. Categorical variables are compared using χ^2 test or Fisher exact test. Continuous data are compared using Student's t-test or Wilcoxon rank test. The primary analysis (evaluating non-inferiority of the PQT) is assessed through hypothesis testing and derivation of a one-sided 95% CIs. P values <0.05 were considered statistically significant.

The following processes are applied to the microbiota distribution of the secondary outcome data: quantitative insights into microbial ecology[20] (QIIME2, https://qiime2.org/) is used to clean and assemble the original offline data. The amplicon sequence variants (ASVs) are assigned to taxa (domain, kingdom, phylum, class, order, family, genus and species) by matching to SILVA database V138. The alpha diversity of gastrointestinal microbiota is based on Shannon's diversity index, observed ASVs, Faith's phylogenetic diversity and Pielou's evenness. Microbiota statistical analyses are performed using R (V.3.6.1 platform; https://www.r-project.org/). Principal coordinate analysis(PCoA) is performed to represent the differences of the beta diversity based on Bray-Curtis, Jaccard distances, weighted unifrac distance and unweighted unifrac distance. The composition of microbiota is compared between different groups, and the different taxa are identified based on linear discriminant analysis(LDA) effect size(LEfSe). Adonis function in R vegan is used to quantify the impact of host lifestyle on microbiome community.

Specimen preservation

Special specimen administrators are designated, for this study, at SCC and the study site to ensure the unified storage of specimens and the management of refrigerator keys. The specimen administrator sorts samples according to their ID number in a sequence. The specimens will be transferred to the SCC in drikold and stored at a temperature of −80°C.

Privacy measures for patient data

All specimens and forms collected as part of this study are coded using unique patient identifiers; electronic data are stored in an encrypted database on a password-protected platform, which can only be identified by authorised research personnel. As well, patient records will be accessed only as per the regulations of the Ethics Research Committee at the SCC, and only when necessary. To the extent permitted by applicable laws and/or regulations, any records relating to patient identification are confidential and will not be made public. Patients or their legal representatives are notified in a timely manner if new information arises that may affect a patient's continued participation in the study.

Ethics and dissemination

This study was approved by the Ethics Committee of Sichuan Cancer Center & Hospital (No. SCCHEC-02-2019-015). Any amendment to the research protocol will be submitted for ethical approval. All participants must provide written informed consent (online supplemental material 1). On completion, the results of the study will be published in the appropriate peer-reviewed journal.

Author affiliations
[1]School of Medicine, University of Electronic Science and Technology of China, Chengdu, China
[2]Center for Cancer Prevention Research, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China
[3]Department of Gastroenterology, Jilin People's Hospital, Jilin, China
[4]Chongqing Medical University, Chongqing, China
[5]West China School of Public Health/West China Fourth Hospital, Sichuan University, Chengdu, China
[6]Department of Cancer Epidemiology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[7]Cancer Prevention and Treatment Office, Yanting Cancer Hospital, Mianyang, China

Acknowledgements We thank all the participants and their advisors involving in this study, especially the health providers in Yanting Cancer Hospital.

Contributors DW, TL, YZ and WC contributed to the study design. ZY, JL and HJ contributed to the data collection. DW, ZS, TL, QT, TC, YL, YZ, WC and YS supervised the field study. DW, ZS and TL drafted the initial manuscript. All authors have reviewed and revised the final manuscript.

Funding This study was supported by Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (CIFMS) (2016-I2M-3-001).

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Dingkun Wu http://orcid.org/0000-0003-1600-9571
Yuqian Zhao http://orcid.org/0000-0002-2736-4766

REFERENCES

1 Warren JR, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983;1:1273–5.
2 Hooi JKY, Lai WY, Ng WK, *et al*. Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. *Gastroenterology* 2017;153:420–9.
3 Zamani M, Ebrahimtabar F, Zamani V, *et al*. Systematic review with meta-analysis: the worldwide prevalence of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2018;47:868–76.
4 Suerbaum S, Michetti P. *Helicobacter pylori* infection. *N Engl J Med* 2002;347:1175–86.
5 Atherton JC. The pathogenesis of *Helicobacter pylori*-induced gastro-duodenal diseases. *Annu Rev Pathol* 2006;1:63–96.
6 McColl KEL. Clinical practice. *Helicobacter pylori* infection. *N Engl J Med* 2010;362:1597–604.
7 Kashimura H, Suzuki K, Hassan M, *et al*. Polaprezinc, a mucosal protective agent, in combination with lansoprazole, amoxycillin and clarithromycin increases the cure rate of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 1999;13:483–7.
8 Goodwin A, Kersulyte D, Sisson G, *et al*. Metronidazole resistance in *Helicobacter pylori* is due to null mutations in a gene (rdxA) that encodes an oxygen-insensitive NADPH nitroreductase. *Mol Microbiol* 1998;28:383–93.
9 Debets-Ossenkopp YJ, Pot RG, van Westerloo DJ, *et al*. Insertion of mini-IS605 and deletion of adjacent sequences in the nitroreductase (rdxA) gene cause metronidazole resistance in *Helicobacter pylori* NCTC11637. *Antimicrob Agents Chemother* 1999;43:2657–62.
10 Rimbara E, Noguchi N, Kawai T, *et al*. Fluoroquinolone resistance in *Helicobacter pylori*: role of mutations at position 87 and 91 of GyrA on the level of resistance and identification of a resistance conferring mutation in GyrB. *Helicobacter* 2012;17:36–42.
11 Hwang TJ, Kim N, Kim HB, *et al*. Change in antibiotic resistance of Helicobacter pylori strains and the effect of A2143G point mutation of 23S rRNA on the eradication of *H. pylori* in a single center of Korea. *J Clin Gastroenterol* 2010;44:1–43.
12 Binh TT, Shiota S, Suzuki R, *et al*. Discovery of novel mutations for clarithromycin resistance in *Helicobacter pylori* by using next-generation sequencing. *J Antimicrob Chemother* 2014;69:1796–803.
13 Guo Y, Zhang Y, Gerhard M, *et al*. Effect of *Helicobacter pylori* on gastrointestinal microbiota: a population-based study in Linqu, a high-risk area of gastric cancer. *Gut* 2020;69:gutjnl-2019-319696.
14 Ferreira RM, Pereira-Marques J, Pinto-Ribeiro I, *et al*. Gastric microbial community profiling reveals a dysbiotic cancer-associated microbiota. *Gut* 2018;67:226–36.
15 Guo M-wei, Liu F-ming, Zhou W. Research progress of 16S rRNA sequencing technology in detection of intestinal flora. *Laboratory Sci* 2019;22:1–4.
16 Almonacid DE, Kraal L, Ossandon FJ, *et al*. 16S rRNA gene sequencing and healthy reference ranges for 28 clinically relevant microbial taxa from the human gut microbiome. *PLoS One* 2017;12:e0176555.
17 Kulich KR, Madisch A, Pacini F, *et al*. Reliability and validity of the gastrointestinal symptom rating scale (GSRS) and quality of life in reflux and dyspepsia (QOLRAD) questionnaire in dyspepsia: a six-country study. *Health Qual Life Outcomes* 2008;6:12.
18 Malfertheiner P, Megraud F, O'Morain CA, *et al*. Management of Helicobacter pylori infection-the Maastricht V/Florence consensus report. *Gut* 2017;66:6–30.
19 Malfertheiner P, Bazzoli F, Delchier J-C, *et al*. *Helicobacter pylori* eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial. *Lancet* 2011;377:905–13.
20 Bolyen E, Rideout JR, Dillon MR, *et al*. Reproducible, interactive, scalable and extensible microbiome data science using QIIME 2. *Nat Biotechnol* 2019;37:852–7.

知情同意书 Informed Consent

尊敬的先生/女生：

Dear Sir/ Madam

您好！我们邀请您参加“不同疗法治疗胃幽门螺杆菌感染的疗效对比及对胃和肠道菌群分布影响的随机对照前瞻性研究”的随机对照临床研究。在您决定是否参加这项研究之前，请您仔细阅读以下内容，帮助您了解该项研究。如果您愿意，您可以向医生询问，以确定您理解有关内容。

You will be invited to participate in a randomized controlled clinical study. Please read the informed consent to help you understand the study before you decide whether to participate in the study or not. If you have any questions, please consult the doctor to make sure you understand the study.

1. 研究目的

1. Objectives

以传统治疗四联铋剂方案为对照，观察含聚普瑞锌四联疗法对胃幽门螺旋杆菌（HP）的根除效果；进行 HP 抗生素耐药突变位点检测，探索含聚普瑞锌四联疗法疗效与耐药位点之间的关系；探索采用不同治疗方法前后，患者胃以及肠道菌群分布情况；探索治疗后，采用不同方案的患者其胃以及肠道菌群分布情况。

The three objectives of the study are as follows. The first is to evaluate the efficacy of polaprezinc-containing quadruple therapy for eradication of *H. pylori* infection. The second is to detect the antibiotic drug-resistance mutation sites of *H. pylori* and explore the association between the therapy and the drug-resistance sites. The third is to compare the distribution of gastral and intestinal flora, before and after the treatments and between the different therapies.

2. 研究背景

2. Background

幽门螺杆菌感染是慢性胃炎的重要病因，根除 HP 是治疗慢性胃炎和预防复发的重要手段。HP 根除治疗方案主要包括三联和四联疗法。随着时间变迁，长时间和频繁应用抗生素出现 HP 对抗生素耐药现象，导致 HP 根除率越来越低，目前阿莫西林和克拉霉素是临床中较为常用的两个抗生素。

H. pylori infection is an important etiology of chronic gastritis, and eradication of *H. pylori* is an essential approach to treat chronic gastritis and prevent its relapse. Therapeutic regimens mainly include triple and quadruple regimens at present. *H. pylori* eradication rates are constantly decreasing, due to secular and frequent use of antibiotics resulting in antibiotic-resistance of *H. pylori* over time.

聚普瑞锌颗粒（商品名：瑞莱生）是唯一一个 L-肌肽与锌的螯合剂，具有多途径阻断幽门螺杆菌的独特药理作用，通过阻断幽门螺杆菌定植、抑制其活性、清除尿素酶及一氯胺、抑制炎症反应达到提高幽门螺杆菌根除率的目的。由吉林省博大伟业制药有限公司研制的聚

普瑞锌颗粒于 2012 年在中国上市。本着严谨、科学循证的态度，在上市后将对其进行深入研究，验证其提高 HP 根除率的有效性。

Polaprezinc, a chelating agent of L-carnosine and zinc, can pharmacologically block the colonization of *H. pylori* by inhibiting its activity and the correlated inflammatory chain reaction, and removing urea, enzymes, monochloramines to eradicate *H. pylori*. Polaprezine Granules produced by Jilin Broadwell Pharmaceutical Co., Ltd was approved in China in 2012. Post-marketing study should be conducted to monitoring its performance in improving *H. pylori* eradication rate.

随着生活质量的提高，生活节奏的加快，HP 阳性的胃炎患者逐年增多，严重者可发展为溃疡甚至胃癌，严重影响患者的生活质量甚至危及患者生命，因而，应及时采取有效的手段进行治疗。目前治疗 HP 阳性胃炎的常用方法为质子泵抑制剂联合两种抗生素，但近年抗生素耐药性明显增加，HP 根除率有所下降。因此，探索 HP 耐药性也是本项目的研究目的之一。

As the quality of life improves, the pace of life accelerates, the number of patients with *H. pylori* positive gastritis increases by years, and the severe cases can develop into ulcers or gastric cancer, which affects the quality of life or even endangers the lives of patients seriously. Therefore, effective means should be taken for *H. pylori* eradication. At present, the commonly used therapy of *H. pylori* positive gastritis is proton pump inhibitor (PPI) combined with two antibiotics, but antibiotic-resistance has been increased recently, and the rate of *H. pylori* eradication has decreased. Hence, exploring *H. pylori* drug-resistance is also one of the objectives of this study.

3. 研究内容和步骤

3. Procedures

如果您是近期诊断为 HP 阳性的患者，同意参加本研究并签署本知情同意书，您将会接受一些检查，包括一般体格检查、心电图、C13/C14 尿素呼气试验、肝肾功、血常规、尿常规、粪便 HP 抗原等，以确定您是否适合参加本项研究，这些检查都是免费的。如果您经过检查，符合入选标准，您将被随机分入治疗组或对照组接受相应治疗。如果您符合本研究入组条件，医生将建议您参与本研究。您将免费得到本品和三联药品的治疗，研究期间医生将严密观察您的治疗情况，让您得到有效的医学治疗和服务。

If you agree to participate in this study when you are recently diagnosed *H. pylori* positive, you will be invited to several examinations including general physical examination, electrocardiogram (ECG), C13/C14 urea breath test, blood test for liver and kidney function, urine test, *H. pylori* stool antigen, etc. These will determine whether you are suitable for this study which are free of charge. If you meet the inclusion criteria, you will be randomized into the treatment/control group. You will receive free treatment of quadruple therapy under the guidance of the doctors during the study.

本研究为随机、对照试验设计。158 例患者有相同可能性分入治疗组（奥美拉唑、阿莫西林、克拉霉素联合聚普瑞锌颗粒）或对照组（奥美拉唑、阿莫西林、克拉霉素联合枸橼酸

铋钾），分别服用试验药或对照药连续治疗 2 周后停药。在接受药物治疗前后，您将进行 2 次免费的无痛胃镜检查，以了解您胃部的疾病或健康状态变化情况；在接受药物治疗的期间，要求您每周定期来医院接受相应的检查，并按要求填写日记卡，交由您的主管医生检查，同时领取您下一周期服用的药物。你必须将在研究期间自行服用的其他药物，以及您打算在该项研究期间使用的药物和疑问告知您的医生。这一点非常重要，如果您不便按照上述要求或者为了您的安全，医生也可能让您退出该项研究，接受其他替代治疗。特别提醒的是，如果您是妊娠妇女，则不宜参加本项研究。育龄妇女应该在试验期间采取有效避孕措施。

This study is a randomized, controlled trial. 158 patients have the same possibility to be assigned into treatment group (esomeprazole, amoxicillin, clarithromycin combined with polaprozinc granules) or control group (esomeprazole, amoxicillin, clarithromycin combined with bismuth potassium citrate). Before and after the therapy, you will have free painless gastroscopy examinations respectively, to observe the stomach. During the course of medication, you are required to come to the hospital after one week for a corresponding examination, and fill in the diary card to submit it to your doctor, and receive the medicine for the next cycle. You should inform the doctor of any other drug you take on your own or intend to use during the study. This is very important, and if you do not follow the requirements above, for your safety, you may be asked to withdraw from the study, and receive alternative treatment. In particular, it is not appropriate to participate if you are pregnant currently. Reproductive women should take effective contraception during the study.

4. **参与本研究的风险**

4. **Risk**

对于 HP 阳性患者，临床主要的治疗方法为质子泵抑制剂联合两种抗生素，本研究中所应用的质子泵抑制剂为阿斯利康制药有限公司生产的奥美拉唑，所选用的抗生素分别为西安利君制药有限责任公司生产的克拉霉素及联邦制药生产的阿莫西林，以及丽珠医药生产的枸橼酸铋钾胶囊。在服用奥美拉唑期间可能出现头痛和腹泻、恶心、便秘等胃肠道症状，其发生率在 1～3%。对成年患者，克拉霉素每天总剂量为 1 克时的最常见不良反应是恶心、呕吐、味觉失调、腹泻、皮疹、胃气胀、头痛、便秘、听觉障碍、白细胞和血小板数减少等。 在服用阿莫西林期间，可能发生的不良反应为恶心、呕吐、腹泻及假膜性肠炎等胃肠道反应；皮疹、药物热和哮喘等过敏反应；贫血、血小板减少、嗜酸性粒细胞增多等；血清氨基转移酶可轻度增高；由念珠菌或耐药菌引起的二重感染；偶见兴奋、焦虑、失眠、头晕以及行为异常等中枢神经系统症状。

The esomeprazole used in this study is produced by AstraZeneca Pharmaceutical Co., Ltd., clarithromycin produced by Xi'an Lijun Pharmaceutical Co., Ltd., amoxicillin produced by United Laboratories Co., Ltd., and bismuth potassium citrate capsule produced by Livzon Pharmaceutical Group Inc. Headache, diarrhea, nausea, constipation and other gastrointestinal symptoms may occur by esomeprazole administration, with the occurrence rate of 1~3%. For adults, the most

common adverse effects of clarithromycin at a total daily dose of 1 g are nausea, vomiting, taste disorders, diarrhea, rash, stomach bloating, headache, constipation, hearing impairment, leukopenia, and thrombocytopenia. During the administration of amoxicillin, the possible adverse reactions are gastrointestinal reactions such as nausea, vomiting, diarrhea and pseudomembranous enteritis; allergic reactions such as rash, drug fever and asthma; anemia, thrombocytopenia, eosinophilia, etc.; serum aminotransferase may be slightly elevated; secondary infections caused by candida or drug-resistant bacteria; and occasional symptoms of the central nervous system include excitement, anxiety, insomnia, dizziness, and behavioral abnormalities, etc.

任何药物均可能产生一定的不良反应，故不能排除本研究参与者研究期间发生不良反应的可能。内镜检查及活检后极少发生上消化道出血。活检后出血是内镜检查的常见并发症，凝血功能正常的情况下，绝大多数无需处理均能自凝。在研究中发现任何可能影响您健康的情况，医生会及时告知您，并积极采取有效的治疗措施。

Adverse reactions may be caused by any drug. Upper gastrointestinal bleeding rarely occurs after endoscopy and biopsy. Bleeding after biopsy is a common complication of endoscopic examination, most of them can self-coagulate without treatment when coagulation function is normal. Any situation that may affect your health founded in the study, the doctor will inform you in time and take effective treatment measures.

5. 研究可能的获益

5. Benefits

本研究将为您提供目前临床用于治疗 HP 感染的药品和相关的检查费用。研究期间，您将获得 2 次免费的高质量无痛胃镜检查，可帮助您及时掌握胃部健康状况。本研究所涉及到的 HP 相关治疗可能有效，也可能无效。根据前期研究，如您完成本项研究的全过程，很可能将得到较好的 HP 根除效果。

This project will provide you with drugs for *H. pylori* eradication and associated examination costs. You will receive 2 free high-quality painless gastroscopy tests. *H. pylori* related treatment involved in this study may be effective or ineffective. According to the previous studies, if you complete the process of this study, it is likely that *H. pylori* eradication should be effective.

6. 研究相关费用及补偿

6. Expense and Compensation

在您参与本研究期间，您所使用的试验药物（聚普瑞锌、奥美拉唑、阿莫西林、克拉霉素药品、铋剂）由研究者免费提供，本研究规定的C13/C14尿素呼气试验、血常规、尿常规、肾功能、肝功能、心电图、尿妊娠检查及粪便HP抗原检查，亦由申办单位支付相关检查费用。与本项研究无关的费用（如：除胃以外的其他部位的病理诊断费用及非HP感染的

其他疾病治疗费用），则由您或您的医疗保险机构负担。在研究期间，如果您发生与本研究药物相关的不良事件或严重不良事件时，医生会采取积极的措施及时进行处理。如发生健康损害时，依据国家法律法规，研究者将对您进行相应的补偿。

The drugs (polaprozinc, esomeprazole, amoxicillin, clarithromycin, bismuth) are free of charge. The $^{13}C/^{14}C$ UBT, blood test for renal function and liver function, urine test, ECG, urine pregnancy test and *H. pylori* stool antigen examination are also paid by the investigators. Expenses irrelated to this study (e.g., the cost of pathological diagnosis of sites other than the stomach and the cost of treatment of other diseases that are not *H. pylori* infection) should be paid by yourself or the medical insurance. If you have adverse events or serious adverse events related to the drugs during the study period, the doctor will take measures in time. In the event of health damage, according to national laws and regulations, researchers will compensate you accordingly.

7. 遵从的义务

7. Obligation

在整个研究期间，您必须遵守本品研究方案的有关规定，配合医护人员，详细记录试验相关的信息资料，保证研究资料的真实性。如果您未经负责医生的同意使用其他药物，或有妨碍研究完成的行为，研究人员可要求您退出试验，或提前终止试验。

During the whole research period, you must abide by the relevant regulations of the research protocol, cooperate with the medical staff, record the relevant information of the study in detail, and ensure the authenticity of the data. If you use other drugs without the consent of the doctor, or if there is an act that hinders the completion of the study, the researcher may ask you to withdraw from the study or terminate the study in advance.

8. 可能获得的其他备选治疗方案及其受益和风险

8. Alternative therapeutic regimens, risks and benefits

HP感染目前临床多采用联合用药来清除HP感染，本研究中含铋剂四联疗法为首选的一线治疗方案。此外，其他备选的治疗方案包括：不包含铋剂的四联疗法、序贯疗法、三联疗法以及包含喹诺酮的治疗方案等。若您不愿意参加本研究，您也可以选择自行咨询医生，针对您的个体情况选择治疗方案。不同治疗方案对清除HP感染均可能有效或无效的。目前临床上HP治疗后的根除率大约在80%。

Combination drugs, usually, are adopted to eradicate *H. pylori* infection at present. The bismuth-containing quadruple therapy is the first-line treatment. In addition, alternative treatment options include quadruple therapy without bismuth, sequential therapy, triple therapy, and treatment with quinolone, etc. If you are not willing to participate in this study, you can also consult the doctor and choose regimen. Different treatments may effective or ineffective in eradicating *H. pylori* infection. At present, the eradication rate in clinical is about 80%.

9. 自愿参加/退出研究

Version：1.3
Date：2019.05.20

9. Voluntary

参与本研究以自愿为原则，您可以拒绝参与或在任何时候均可退出，您将不会因此受到任何惩罚或受到任何不公正待遇。如果您计划退出研究，必须通知研究医生。如果继续参加本研究对您不利，医生有权在任何时候终止您参与本研究。伦理委员会及申办单位也有可能终止本研究。如果提前退出研究，医生将要求您做最后一次检查和评估。在相关法律/法规允许范围内，退出之前已获得的研究资料仍可能会被采用。如果您对本研究有疑问，请联系四川省肿瘤医院医学伦理委员会，电话028-85420681。

Participation in this study is voluntary and you could refuse to participate or withdraw at any time and there will not be any punishment or unfair treatment. You should inform the doctor if you plan to withdraw the study. If this study is detrimental to you for continuing to participate in, the physician has the right to terminate your participation in this study at any time. The ethics committee and the investigators may also stop this study. The doctor will ask you to do the exit examinations before you withdraw from the study. Data obtained prior to withdrawal may still be used under the relevant laws/regulations. If you have any questions about this study, please contact the Medical Ethics Committee of Sichuan Cancer Hospital at 028-85420681.

10. 医疗记录的公开及保密

10. Privacy issue

在有关法律规定下，您的医疗记录将被编码后妥善保存，但研究人员、监查人员、伦理委员会成员或药政管理人员可能查阅您的医疗记录。如果研究结果需要公开发表，您的身份不会被公开。签署本文件表示您已经授权研究人员可以使用您研究相关的医疗记录。

Your personal data in and during the study are confidential, but researchers, inspectors, members of the ethics committee or drug administration may refer to your personal data in the research unit as required. No information about you will be disclosed if the results of this study are published. Signing this document indicates that you have authorized the researchers to use your medical data.

您同意在本研究中获得的资料，包括所有检查结果保存在研究者的计算机和书面文档系统中，研究资料中不会出现您的姓名。您也同意将这些试验资料用于在我国或其它国家药品注册的目的，在此过程中申办单位将使用这些记录，并按有关法律法规规定予以保存。

Your file obtained in this study, including all examination results, is kept in the researcher's computer and paper documents, and your name will be covered in data. These data may be used for registration in China or other countries. In the process, the sponsors will use these data and save them in accordance with the relevant laws and regulations.

Version：1.3
Date：2019.05.20

我们将储存本项目所采取的活检标本及胃液，粪便等样本，并可能在以后的研究中使用，所有活检标本及胃液，粪便样本上贴有带编码的标签，不会出现您的姓名，您的所有信息将会保密。

The biopsy specimens, gastric juices, stools and other samples collected in this study will be stored and may be used in future studies. All specimens are labeled with codes not appear your name. All your information will be kept confidential.

如果您对本项目还有其他的疑问，可以联系您当地_____医院的医生_____，电话：_____，您也可以联系本研究的负责人，_____医院_____教授，电话:_____。

If you have any question about this study, you can contact_____ hospital doctor_____ at: _____, you can also contact the principal investigator(PI), _____ hospital professor_____ at: _____.

Version：1.3
Date：2019.05.20

知情同意书Informed Consent

患者（或代理人）姓名：

Patient's (or Patient's Families) name:

- 我在此确定医生已向我告知了聚普瑞锌颗粒临床研究的目的、方法、获益和可能的风险。
- I confirm that the doctor informed me the purposes, methods, benefits and risks of the polaprezinc granules clinic study.
- 我已经阅读并理解了关于受试者资讯的说明。
- I have read an informed consent form.
- 我已经知道研究的结果将在临床研究总结报告中进行分析，但个人资料如：姓名、生日和诊断结果等会保密。
- I know that the results of the study will be analyzed in clinic research report, but personal data such as name, birthday and results of diagnosing are confidential.
- 我可以在任何时候退出该项研究。
- I can choose to quit this study at any time.
- 我有足够的机会提出问题并表明我是否自愿参加该项研究。
- I have the opportunity to ask questions and to indicate whether I volunteered to participate in the study.
- 我已被告知口服该药可能发生不良反应，如在试验过程中发生与试验有关的不良反应研究单位和申办者将给予积极的治疗。
- I have been told that oral administration of the drug may have adverse reactions, research institution and the applicant will take active treatment measures if the adverse reactions related to the trial occurred during the study.
- 我同意在试验期间采取适当的避孕措施（育龄妇女）。
- I agree to take appropriate contraception during the trial (reproductive women)
- 我已知道本项研究已经得到本医院伦理委员会讨论批准。
- I know that this project has been approved by the ethics committee of Sichuan Cancer hospital.

本知情同意书一式两份，请受试者和研究中心妥善保管，以备药品注册审评部门审查。

This informed consent form is in duplicate and should be kept properly by the subject and the research center for review by the drug registration review department

患者（或代理人）：我已阅读并完全理解上述的有关医学研究的资料，我确认已有充足的时间考虑，有关疑问已经得到圆满解答，我自愿同意参加本临床研究。

Patient's (or Patient's Families): I have read and fully understood the above information on medical research, I confirm that all questions have been answered, and I voluntarily agree to participate in this clinical study after consideration.

Version：1.3
Date：2019.05.20

患者（或代理人）姓名： **与患者关系：**

Patient's (or Patient's Families) name: Kinship:

日期： 年 月 日

Date:

联系电话：1、手机： **2、宅电：**

Telephone:

家庭住址：

Address:

主管医生：我确认已向患者解释了本项研究的详细情况，包括其权利及可能的获益和风险；并且保证随时解答患者关于本项临床研究信息的咨询。

Doctor: I confirm that I have explained to the patient the details of this study, including its rights, possible benefits and risks; and assure to answer the patient's consult on this clinical study at any time.

医生签名：

Doctor Name:

日期： 年 月 日

Date：

联系电话：

Telephone:

Version：1.3
Date：2019.05.20