# Comparison between optimized bismuth quadruple therapy and standard clarithromycin-based triple therapy for first-line *Helicobacter pylori* eradication: a double-blind randomized controlled trial

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The Lancet Regional Health - Americas 2026;53: 101312

Published Online 22 November 2025
https://doi.org/10.1016/j.lana.2025.101312

## Summary

**Background** ***Helicobacter pylori*** **eradication reduces the risk of peptic ulcer disease and gastric cancer. In Chile, the effectiveness of standard triple therapy has dropped below 80%. We compared *optimized bismuth quadruple therapy*: esomeprazole 40 mg three times a day, amoxicillin 1 gr three times a day, metronidazole 500 mg three times a day, and bismuth subsalicylate 369 mg three times a day for 14 days, and standard triple therapy omeprazole 20 mg twice a day, amoxicillin 1 gr twice a day, and clarithromycin 500 mg twice a day for 14 days in a Chilean population.**

**Methods** **Randomized double-blind clinical trial. 127 treatment-naïve individuals with confirmed active *H. pylori* were recruited. The primary outcome was successful *H. pylori* eradication, at least 4 weeks post-treatment. We assessed *H. pylori* resistance to clarithromycin and participants' *CYP2C19* genotype/phenotype. We compared eradication success between the groups using intention-to-treat and per-protocol analyses. The trial adhered to CONSORT guidelines. NTC-Number: NCT05664685 (trial completed).**

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**Disclaimer**: This summary is available in Spanish in the Supplementary Material.

**Findings** 127 participants were recruited and randomized (64 standard triple therapy, 63 optimized bismuth quadruple therapy). Men were 44% (56/127), and the mean age was 48 (standard deviation: 14.2) in the sample. Baseline characteristics between the two groups were similar. In intention-to-treat analysis, optimized bismuth quadruple therapy had a significantly higher eradication rate versus standard triple therapy: 95% (60/63) [95% CI 86%–99%] vs. 81% (52/64) [70%–89%], p = 0.033. Adverse events were comparable: optimized bismuth quadruple therapy 67% (42/63) [54%–77%] vs. standard triple therapy 66% (42/64) [53%–76%], p = 1.00. There was no difference in baseline clarithromycin resistance or *CYP2C19* polymorphisms.

**Interpretation** Optimized bismuth quadruple therapy eradication is higher than standard triple therapy in treatment-naïve individuals with active *H. pylori*, without difference in adverse events or adherence. Optimized bismuth quadruple therapy is a reliable and safe empiric eradication therapy, especially in areas with high clarithromycin resistance.

**Funding** FONDECYT (1230504 AR); ANID-FONDAP (152220002 AR); Horizon 2020 program of European Union (825832 AR); ANID-FONDAP (15130011).



**Keywords:** *Helicobacter pylori*; Antibiotics; Bismuth quadruple therapy; Standard triple therapy; PPI

## Research in context

### Evidence before this study

MEDLINE and EMBASE, searched in July 2022 using terms and synonyms for "Helicobacter pylori", "treatment or eradication", and "Latin America". The electronic search was complemented by a hand-search of bibliographies from key articles identified and a review of major clinical trial registries for ongoing studies. *Helicobacter pylori* infection is a significant public health issue, especially in Latin America, where the prevalence of infection is very high. This region also faces disproportionately high rates of complications, including gastric cancer. In Chile, the effectiveness of standard triple therapy for *Helicobacter pylori* eradication has declined to unacceptable levels. Eradication therapy failure with standard triple therapy is primarily due to antibiotic resistance to clarithromycin and metabolic variations in proton pump inhibitor metabolism mediated by *CYP2C19* polymorphisms and treatment adherence. Many studies have highlighted the need for alternative treatments, such as bismuth quadruple therapy, which has shown effectiveness in real-world studies in Latin America but has not been evaluated in randomized clinical trials.

### Added value of this study

This trial provides new insights into the comparative effectiveness of an optimized bismuth quadruple therapy vs. standard triple therapy in a Chilean population for *Helicobacter pylori* infection. We ensured robust results using a randomized, double-blind clinical trial design and accounting for baseline clarithromycin resistance and *CYP2C19* polymorphisms. Our findings demonstrate that optimized bismuth quadruple therapy significantly outperforms standard triple therapy in eradicating *Helicobacter pylori*, with eradication rates of 95% (60/63) [95% CI 86%-99%] for optimized bismuth quadruple therapy compared to 81% (52/64) [70%-89%] for standard triple therapy in the intention to treat analysis. Mild-moderate adverse events were common but not different between the groups (optimized bismuth quadruple therapy: 67% (42/63) vs. standard triple therapy: 66% (42/64)). This trial highlights the importance of considering local antibiotic resistance patterns and optimizing treatment regimens accordingly. Moreover, this trial is consistent with prior reports of extensive proton pump inhibitors metabolizer phenotype prevalence and high clarithromycin resistance.

### Implications of all the available evidence

The results of this trial confirm that optimized bismuth quadruple therapy should be used as a preferred first-line empiric therapy for *Helicobacter pylori* eradication in Chile or other countries with similarly high clarithromycin resistance (>15%). For clinicians, this trial supports the adoption of optimized bismuth quadruple therapy as a more effective and reliable empiric treatment option and confirms that standard triple therapy should be removed as an empiric option. For payors, optimized bismuth quadruple therapy should be the preferred coverage option. Future research should focus on continuous surveillance of antibiotic resistance patterns and further optimization of eradication therapies to maintain high success rates and maximize tolerance and adherence. This trial contributes to the growing evidence advocating tailored treatment strategies based on regional resistance profiles and other population considerations.

## Introduction

*H. pylori* (*H. pylori*) is an infectious carcinogen globally. Recent studies estimate the worldwide prevalence of *H. pylori* infection is 44%,[1] with wide variation depending on the country and population. Latin America has a particularly high burden of *H. pylori*[2] and, in Chile, the prevalence of infection is estimated at around 73% [95% CI 70%–76%] in 2002[3] measured in the National Health Survey (n = 2617). Fortunately, the prevalence seems to be decreasing. Another large study in Chile from a single Health Center in Santiago de Chile (n = 11,355) confirmed this trend, reporting a decline in prevalence from 45% in 2010 to 29% in 2020.[4]

*H. pylori* is uniquely adapted to colonize the surface of the stomach and invariably causes chronic gastritis unless successfully eradicated.[5] Most carriers are asymptomatic; however, 1–10% will develop duodenal or gastric ulcers, 0.1%–3% gastric cancer, and <0.01% mucosa-associated lymphoid tissue lymphoma.[6] *H. pylori* eradication treatment is recommended for all adults with an active infection, barring contraindications.[7]

Successful eradication is associated with a substantially reduced risk of associated complications. Indeed, a recent meta-analysis of 10 randomized controlled trials demonstrated an approximately 50% reduction in the risk of both incidents and metachronous gastric cancer.[8] However, eradication failure is increasing and places individuals at continued risk of complications from persistent *H. pylori* infection. Moreover, eradication failure compromises antibiotic stewardship,[7] which substantially increases healthcare costs, as it requires alternative treatment regimens with high-dose acid suppression and antibiotics, not to mention the inconvenience and the impact on the quality of life of patients. Recognizing the health implications as well as preventability, the World Health Organization (WHO) recognizes *H. pylori* eradication failure as a significant public health problem in need of immediate attention in its list of antibiotic-resistant *"priority pathogens"*.[9]

Recognizing the high burden of *H. pylori* infection, the Chilean government provided financial coverage for eradication therapy to all diagnosed adults[10]; however, standard triple therapy (STT) remains the recommended regimen despite low and decreasing eradication rates, based on historically achieved acceptable, albeit still not ideal, eradication rates.[11] In Chile, the effectiveness of STT is decreasing from an 86% reported rate of successful eradication in a randomized controlled trial performed in 2009–2010, which included Chile, Colombia, Costa Rica, Honduras, Nicaragua, and Mexico[11] to 64% reported in 2018 by Arenas et al. in Santiago, Chile.[12]

The main reasons for *H. pylori* eradication failure are the strain resistance to antibiotics, especially clarithromycin, the insufficient gastric acid suppression related to the rapid metabolism of Proton Pump Inhibitors (PPI) mediated by *CYP2C19* extensive metabolizer genotypes,[13] and the nonadherence to therapy among patients.[14] In Chile, a 2019 study also shows a prevalence in *H. pylori* clarithromycin resistance of 26%, and clarithromycin resistance was associated with 87% lower odds of eradication (Odds Ratio 0.13) [0.04–0.49].[12]

International guidelines in *H. pylori* eradication, such as the Maastricht Guidelines and 2024 American College of Gastroenterology Guidelines, recommend bismuth quadruple therapies and, ideally, optimized bismuth quadruple therapy (o-BQT) as the first-line preferred regimen, especially in places with unknown or high (>15%) prevalence of *H. pylori* clarithromycin resistance.[13] In 2023, the initial report of the "Latin American registry on the management of *H. pylori* infection", which is a non-randomized observational real-world registry, reported eradication rates of 75% for STT (n = 301) and 100% for bismuth quadruple therapies (n = 57) in Argentina, Chile, Colombia, Costa Rica, Mexico, and Peru.[15] In a recent study, Reyes et al. analyzed eradication and adverse events rates of the most commonly used *H. pylori* eradication schemes in a retrospective cohort design, including 523 participants.[16] The study reported an eradication rate of 98% for bismuth quadruple therapy versus 82% for STT. In this study, the most commonly used bismuth quadruple therapy regimen was esomeprazole 40 mg three times a day, amoxicillin 1 g three times a day, metronidazole 500 mg three times a day, and bismuth subsalicylate 369 mg three times a day. It is important to note that in Chile, tetracycline use is limited compared to North America and Europe.[17] For this reason, bismuth quadruple therapy therapies in Chile use amoxicillin instead of tetracycline.

There is a lack of experimental information on the effectiveness of bismuth quadruple therapy or o-BQT in Chile and Latin America. To fill this important knowledge gap, we designed and conducted a multicentric randomized controlled trial across a health network in Chile to compare o-BQT to STT. The overarching goal is the comparison of optimized bismuth quadruple therapy: esomeprazole 40 mg three times a day, amoxicillin 1 gr three times a day, metronidazole 500 mg three times a day, and bismuth subsalicylate 369 mg three times a day for 14 days, and standard triple therapy omeprazole 20 mg twice a day, amoxicillin 1gr twice a day, and clarithromycin 500 mg twice a day for 14 days in a Chilean population.

## Methods

### Ethics statement

This randomized controlled trial adheres to all ethical standards and guidelines for good research practices. The trial was approved by the Health Sciences Ethical

Board in UC-Chile (original name: *Comité Ético Científico de Ciencias de la Salud*), ID 220710002, ensuring that all procedures comply with the Declaration of Helsinki. Informed consent was obtained from all participants prior to their participation in the study.

Also, it is recorded on Clinicaltrials.gov, with the corresponding NTC Number: NCT05664685, the state of the study is completed. This trial adheres to CONSORT guidelines[18]; the checklist is available in the Supplementary Material.

### Trial design

We performed a double-blind randomized controlled trial with two parallel treatment groups to compare *H. pylori* eradication success rates between an o-BQT vs. STT in a Chilean population (primary outcome). We secondarily aimed to describe and compare adverse events and the therapeutic adherence between o-BQT versus STT.

We recruited participants in 2 Health Centers belonging to UC-CHRISTUS Health Network located in the City of Santiago de Chile, the country's capital with a population of 6 million inhabitants. The UC-CHRISTUS Health Network is a robust integrated health system network that includes two academic hospitals, several outpatient centers, and four endoscopy centers. In this trial, participants were recruited from the endoscopy units of the *Marcoleta Medical Specialties Center* and the *San Joaquín Medical Center*. These centers serve people from both the public and private healthcare systems in Chile, with a higher presence of the middle socioeconomic sector residing in Santiago.

### Participants

Eligible individuals were aged 18–75 years undergoing an elective outpatient esophago-gastro-duodenoscopy. The participants went through the informed consent process before the esophago-gastro-duodenoscopy in a scheduled meeting with a member of the research team the following day of the procedure. Those patients who were found to have *H. pylori* infection based on positive rapid urease test (ProntoDry ®; France), and not previously treated (i.e., *H. pylori* treatment-naïve) were considered eligible for the trial. Indications for esophagogastroduodenoscopy included both diagnostic and/or surveillance (e.g., surveillance of Barrett's esophagus or gastric intestinal metaplasia), irrespective of symptoms, and the referral to esophagogastroduodenoscopy was based on the referring physician's clinical decision-making. We intentionally recruited participants scheduled for esophagogastroduodenoscopy procedures so that we could test for antimicrobial resistance using gastric biopsies confirmed to be positive on rapid urease tests.

Exclusion criteria included pregnant or lactating women, individuals with a history of adverse events to penicillin, salicylates, or PPI class of medications, use of antibiotics or bismuth in the last 4 weeks, a history of gastrointestinal bleeding in the past 12 weeks, a history of current or prior gastric cancer of any stage, any gastric surgery including bariatric surgery, chronic kidney disease in stage 3 or higher, serious or benign malignant diseases with less than 1-year life expectancy, *Clostridioides difficile* infection, or inflammatory bowel disease.

### Interventions

The two arms in this trial were the intervention arm, o-BQT, and the "control" treatment arm, STT, which was the reference. STT consisted of omeprazole 20 mg twice a day dosed 30 min before meals, amoxicillin 1 gr twice a day (MintLab Laboratory, Santiago de Chile), and clarithromycin 500 mg twice a day for 14 days (Andrómaco Laboratory, Santiago de Chile), following current Chilean guideline recommendations.[19] The intervention group o-BQT consisted of esomeprazole 40 mg three times a day dosed 30 min before meals, amoxicillin 1 gr three times a day (MintLab Laboratory), metronidazole 500 mg three times a day (Metropast ®, Pasteur Laboratory), and bismuth subsalicylate 369 mg three times a day for 14 days (Gastroaliv ®, Maver Laboratory, Santiago de Chile), which was demonstrated be effective in a previous non-randomized trial in a Chilean population.[16]

### Allocation, randomization, and blinding

Individuals who met full inclusion criteria were randomized 1:1 to the treatment arms. For the random assignment and keeping the double-blinded execution of the trial, we made a control/intervention sequence by simple randomization of all treatments. The control and intervention containers were identical and were individually labeled with a consecutive numeric code on the outside. We included placebo identical to bismuth pills in the STT group to ensure the same number of pills counts between the groups and to maintain blinding. Thus, both groups had four medications in the container: amoxicillin, metronidazole, esomeprazole, and bismuth in the o-BQT group, and amoxicillin, clarithromycin, placebo, and omeprazole in the STT group.

The treatment containers were delivered to participants according to the order in which they were recruited. The randomization and allocation protocol were executed by an external team composed of clinical pharmacists without participation or knowledge of the trial.

### Measures

The primary outcome was *H. pylori* eradication success, as confirmed by a negative post-treatment urea breath test. Urea breath test was obtained in all participants at least 4 weeks after the end of the therapy, performed in the UC-CHRISTUS endoscopy unit at *Centro de Especialidades Médicas*, using BreathID® Smart urea breath

test platform for *H. pylori* detection (Meridian Bioscience, Cincinnati, OH). Using 13C-labeled urea is considered a positive test for *H. pylori* when, after ingestion of 50 mg of 13C-Urea dissolved in 80 ml of cold water, the difference (DOB) of the δ 0/00 measurements of 13C–CO2 in the exhaled breath sample at t = 30, minus the δ 0/00 of 13C–CO2 in the sample at t = 0, is $\geq$ 4.0 ± 0.4; the sensitivity and specificity of 13C- urea breath test is 99% and 100%, respectively. We explicitly advised participants to discontinue any use of antibiotics or bismuth therapy 4 weeks before testing, and PPI at least 14 days before the scheduled follow-up to minimize any possibility of a false negative urea breath test.

At the 14-day scheduled follow-up, we administered a questionnaire assessing adherence to treatment and the occurrence of adverse events. For adherence, we classified the participants according to their self-reported percentage of dosages taken (<80%, 80%–89%, 90%–99%, 100%). We considered full adherence when exceeding 90%. Regarding adverse events, we specifically asked if, since the beginning of the treatment, the participant developed new or worsened bloating, abdominal pain, bitter taste, constipation, diarrhea, dizziness, dyspepsia, epigastric pain, halitosis, headache, loss of appetite, nausea, vomiting, oral ulcers, skin rashes, drowsiness, or any other symptoms not otherwise specified in the questionnaire. Also, we recorded any symptoms reported by participants spontaneously by phone calls to the research team during the treatment period. We recorded any serious adverse event, defined as those leading to treatment discontinuation, hospitalization, significant morbidity as deemed by the research team, or death.

We bio-banked the gastric mucosa from rapid urease test to measure the baseline *H. pylori* antibiotic resistance to clarithromycin. Clarithromycin point mutations A2142G and A2143G of the *H. pylori* 23s rRNA gene were determined by PCR-RFLP as previously described.[20] Briefly, DNA was extracted from frozen rapid urease test biopsies using the QIAamp DNA mini kit (QIAGEN, Hilden, Germany). First, we performed PCR-based amplification of 23 S rRNA gene followed by restriction enzyme digestion with enzymes BbsI (for A2142G detection) and BsaI (for A2143G detection). 23 S-rRNA amplicons and digested products were separated on 2% or 3% agarose gels, respectively, and were run in parallel with mutant-specific DNA controls. We classified the strains of *H. pylori* as resistant baseline clarithromycin if there was any mutation related to resistance. Participants with lower DNA quality were excluded. These analyses were performed in collaboration with the laboratory of the Department of Pediatric Gastroenterology and Nutrition, School of Medicine, Pontificia Universidad Católica de Chile.

All consented participants also provided a venous blood sample for *CYP2C19* genotyping using a Vacutainer ® system. We classified participants as poor, normal, intermediate, rapid, and ultra-rapid metabolizer phenotypes according to the method described by Lima et al. in the *Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 and Proton Pump Inhibitor Dosing.*[21] Genotyping was performed from the DNA extracted from the buffy coat extracted from blood sample using *TaqMan*® assays from the Drug Metabolism Genotyping Assay (Thermofisher Scientific, USA) to detect *2 (c.681G > A; rs4244285), *3 (c.636G > A; rs4986893) and *17 (–806C > T; rs12248560) variants. These analyses were performed in collaboration at the Laboratory of Chemical Carcinogenesis and Pharmacogenetics, Department of Basic and Clinical Oncology, Faculty of Medicine, University of Chile.

The baseline characteristics of the participants were assessed using a questionnaire before randomization, including sex, age, self-reported per capita family income, weight, height, self-reported smoking status (current, former, never), self-reported comorbidities, clarithromycin resistance, and *CYP2C19* polymorphism.

## Statistical methods

### *Sample size calculation*

We expected at least a 20% difference in the eradication rates between STT and o-BQT, being 70% and 90%, respectively, based on prior literature.[12,16] Using a power of 80% and a two-tailed alpha of 0.05, the minimum sample size required was 62 participants per arm. To account for a possible attrition rate of 5%, we aimed to enroll 65 participants per arm.

### *Descriptive analysis*

We described the participants' baseline characteristics, adherence, and adverse reactions to treatment, using percentages for categorical variables and means with standard deviation or medians with interquartile range for continuous variables. The following variables were evaluated as continuous variables: age, per capita income, and body mass index; while smoking (current/former vs. never), sex (male/female), age group (18–29/30–39/40–49/50–59/60–69/70–75), and diagnosis of diabetes mellitus were evaluated as categorical variables. We also compared the prevalence of *H. pylori* resistance to clarithromycin and the CYP2C19 metabolizer phenotype between groups.

### *Primary outcomes*

The proportion of success was the number of participants in each treatment arm with a negative urea breath test divided by the total number of participants in the arm; people who lost to follow-up were considered treatment failures. We used Fisher's Test for categorical variables to evaluate the differences between treatment arms. The two-tailed p-value test was obtained by doubling the exact one-tailed probability.

We conducted both *intention-to-treat and per-protocol analyses*. All participants were included in the intention-to-treat analysis and evaluated according to their assigned randomized group, irrespective of adherence. In our trial, loss of follow-up was defined as any randomized participant who did not complete the post-treatment urea breath test, irrespective of adherence. These participants were assigned as treatment failures to be conservative in the intention-to-treat. In the per-protocol analysis, we only analyzed individuals who completed at least 80% of their assigned treatment.

We evaluated the between-group treatment efficacy using relative risk and absolute difference, adverse events, and adherence using the Fisher test. We calculate the risk ratio of successful eradication according to the different variables including clarithromycin resistance, adherence, and CYP2C19 metabolizer status for their association with eradication failure. We report the confidence interval at 95% calculated by Clopper/Pearson method and report p-values. We considered p values $< 0.05$ statistically significant. All analyses were performed with the trial investigators still blinded to the treatment assignment group. Analyses were performed using R 4.3.3,[22] Stata 15[23] and the Application JavaStat.[24] There were no major protocol deviations; however, some modifications were made compared to the initial ClinicalTrials.gov registration to enhance the trial's clinical relevance and methodological rigor. First, the follow-up period to assess the primary outcome, *H. pylori* eradication, was adjusted from the 8–12 weeks stated in the protocol to 4 weeks post-treatment. This change better reflects current clinical practice and is in accordance with the Maastricht VI/Florence consensus report. Second, the assumed eradication rates for the sample size calculation were updated from the initial protocol's estimates of 82% vs. 97% to the more realistic figures of 70% vs. 90% used in the final manuscript, based on recent local data. Finally, variables measured at baseline prior to randomization, specifically clarithromycin resistance and the CYP2C19 metabolizer phenotype were reclassified. Although listed as secondary outcomes in the protocol, they are presented as baseline characteristics in this manuscript to accurately reflect that they were not influenced by the trial interventions.

### Role of the funding source statement

The funding sources did not have any role in the design, execution, or data analysis in the trial.

## Results

We assessed 167 persons to include in the study and recruited and consented 127 participants (38 didn't met the inclusion criteria and 2 declined to participate) between October 2022 and November 2023, all of whom underwent randomization (Fig. 1). Of the 64 participants assigned to STT and 63 assigned to o-BQT, only

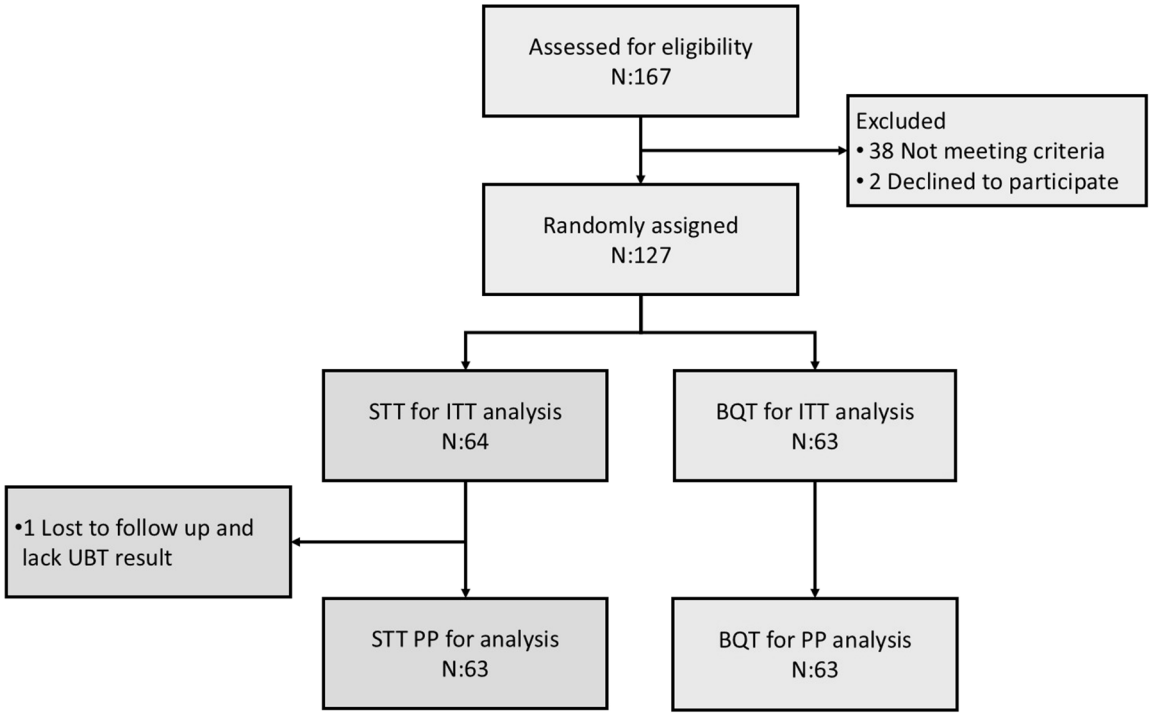


***Fig. 1:*** Flowchart of participants in this RCT (Randomized Clinical Trial). STT: Standard triple therapy; o-BQT: Optimized Bismuth quadruple therapy; UBT: Urea Breath Test.

one person in the STT group lost to follow-up (1% overall).

Baseline characteristics, including sex, age, body mass index, current smoking, diabetes mellitus, and income, are described in Table 1. 98% (125/127) of participants reported an adherence above 80%, 98% in STT (63/64) and 98% in o-BQT (62/63), 91% (115/127) above 90%, being 90% in STT (58/64) and 94% in o-BQT (59/63), and 100% adherence for 76% of the participants, 75% (47/64) for STT and 81% (51/63) for o-BQT. There was no statistically significant difference in adherence overall between the o-BQT and STT groups (p = 0.75).

Clarithromycin resistance analysis on gastric mucosa was successfully performed in 111 (88%) participants; this could not be performed on the remaining 15 (12%) due to insufficient DNA quality. From this subset, 17% of participants showed *H. pylori* clarithromycin resistance, with 18% in STT and 17% in o-BQT. In this cohort, all clarithromycin resistance was due to the A2143G point mutation of the *H. pylori* 23 S subunit. *CYP2C19* genotype analysis was successfully performed in 99% (121). Based on the polymorphism data, intermediate metabolizers were 16%, rapid 13%, and ultrarapid metabolizers 2%. A detailed description of the clarithromycin resistance and PPI phenotypes can be found in Table 1.

Based on intention-to-treat analysis, o-BQT achieved a higher eradication success rate vs. STT 95% (60/63) [86%–99%] vs. 81% (52/64) [70%–89%], p = 0.033 (Table 2). Per-protocol analysis was similar to intention-to-treat analysis results: 95% (60/63) [86%–99%] with o-BQT vs. 81% (51/63) in STT [69%–89%]; p = 0.025 (Table 2). o-BQT had a 1.17 [1.014–1.27] in intention-to-treat analysis and 1.17 [1.016–1.27] in per-protocol analysis higher risk ratio for eradication treatment success compared to STT. The absolute risk difference in the eradication rates was 14% in both intention-to-treat [1%–20%] and per-protocol [1%–21%] analysis (Table 2).

Mild to moderate adverse events were common (see Table 3), but neither clinically nor statistically significantly different between the groups, STT 66% (42/64) vs. o-BQT 67% (42/63), (p = 1.00). The most frequently reported symptoms were bitter taste, diarrhea, abdominal distension, and epigastric pain. There were no serious adverse events in both groups.

## Discussion

The two-arm double-blinded randomized controlled trial results demonstrate that o-BQT achieves higher eradication rates vs. STT in treatment-naïve individuals with confirmed active *H. pylori* infection. The eradication is notably high for o-BQT vs. STT, 95% (60/63) vs. 81% (52/64) in intention-to-treat analysis, and while side effects were common, this did not impact treatment adherence, which was excellent at >95% (121/127). This is the first randomized controlled trial to evaluate the treatment outcomes and experience with o-BQT vs. STT in a Latin American population.

| Variable | Overall | STT | o-BQT |
|---|---|---|---|
| **N per group** | 127 | 64 | 63 |
| **Sex, Male, % (n/N)** | 44% (56/127) | 49% (31/64) | 40% (25/63) |
| **Age, mean (SD)** | 47.6 (14) | 46.5 (14) | 48.8 (15) |
| **Age range** | | | |
| 18–29, % (n/N) | 12% (15/127) | 14% (9/64) | 10% (6/63) |
| 30–39, % (n/N) | 18% (23/127) | 18% (11/64) | 19% (12/63) |
| 40–49, % (n/N) | 25% (31/127) | 27% (17/64) | 22% (14/63) |
| 50–59, % (n/N) | 20% (25/127) | 19% (12/64) | 21% (13/63) |
| 60–69, % (n/N) | 18% (23/127) | 18% (11/64) | 19% (12/63) |
| 70–75, % (n/N) | 7% (9/127) | 5% (3/64) | 10% (6/63) |
| **Per capita income, USD per month, median (Q1—Q3)** | 500.0 (326–1100) | 500.0 (306–917) | 500.0 (407–1222) |
| **Body mass index, mean (SD)** | 28.8 (5.8) | 29.4 (6.7) | 28.2 (4.9) |
| **Active smoking, n (%)** | 14% (18/127) | 18% (11/64) | 11% (7/63) |
| **Diabetes mellitus, n (%)** | 7% (9/127) | 3% (2/64) | 11% (7/63) |
| **CYP2C19 metabolizer phenotype** | | | |
| Poor % (n/N) | 1% (1/127) | 0% (0/64) | 2% (1/63) |
| Normal % (n/N) | 69% (83/127) | 71% (42/64) | 67% (41/63) |
| Intermediate % (n/N) | 16% (19/127) | 20% (12/64) | 11% (7/63) |
| Rapid % (n/N) | 13% (15/127) | 9% (5/64) | 16% (10/63) |
| Ultrarapid % (n/N) | 2% (2/127) | 0% (0/64) | 3% (2/63) |
| **Antimicrobial resistance CLA, % (n/N)** | 17% (19/111) | 18% (10/57) | 17% (9/54) |

STT: Standard triple therapy o-BQT: Bismuth quadruple therapy.

***Table 1:*** **Baseline characteristics of participants.**

| Adverse events | STT | | o-BQT % (N/N) | | p-value[a] |
|---|---|---|---|---|---|
| | N | % [95% CI] | N | % [95% CI] | |
| Any adverse events | 42/64 | 66% [53%–76%] | 42/63 | 67% [54%–77%] | 1.00 |
| Bitter taste | 26/64 | 41% [30%–53%] | 24/63 | 38% [27%–50%] | 0.86 |
| Diarrhea | 13/64 | 21% [12%–32%] | 16/63 | 25% [16%–37%] | 0.67 |
| Abdominal distension | 8/64 | 13% [7%–23%] | 19/63 | 30% [20%–42%] | 0.029 |
| Epigastric pain | 8/64 | 13% [7%–23%] | 12/63 | 19% [11%–30%] | 0.47 |
| Dyspepsia | 9/64 | 14% [8%–25%] | 9/63 | 14% [8%–25%] | 1.00 |
| Dizziness | 5/64 | 8% [3%–17%] | 8/63 | 13% [7%–23%] | 0.56 |
| Headache | 5/64 | 8% [3%–17%] | 6/63 | 10% [4%–19%] | 1.00 |
| Anorexia | 3/64 | 5% [3%–13%] | 8/63 | 13% [7%–23%] | 0.21 |
| Vomiting | 2/64 | 3% [1%–11%] | 8/63 | 13% [7%–23%] | 0.095 |
| Halitosis | 4/64 | 6% [3%–15%] | 6/63 | 10% [4%–19%] | 0.74 |
| Constipation | 4/64 | 6% [3%–15%] | 4/63 | 7% [3%–15%] | 1.00 |
| Drowsiness | 2/64 | 3% [1%–11%] | 3/63 | 5% [2%–13%] | 1.00 |
| Skin Rash | 2/64 | 3% [1%–11%] | 0/63 | 0% [0%–6%] | 0.48 |
| Dry mouth | 1/64 | 2% [0%–8%] | 1/63 | 2% [0%–8%] | 1.00 |
| General discomfort | 0/64 | 0% [0%–6%] | 1/63 | 2% [0%–9%] | 1.00 |
| Erectile dysfunction | 0/64 | 0% [0%–6%] | 1/63 | 2% [0%–9%] | 1.00 |
| Urinary infection | 1/64 | 2% [0%–8%] | 0/63 | 0% [0%–6%] | 1.00 |
| Fungal infection | 1/64 | 2% [0%–8%] | 0/63 | 0% [0%–6%] | 1.00 |
| Antibiotic-associated diarrhea | 0/64 | 0% [0%–6%] | 1/63 | 2% [0%–8%] | 1.00 |
| Fever | 1/64 | 2% [0%–8%] | 0/63 | 0% [0%–6%] | 1.00 |
| Weakness | 1/64 | 2% [0%–8%] | 0/63 | 0% [0%–6%] | 1.00 |
| Reflux | 1/64 | 2% [0%–8%] | 0/63 | 0% [0%–6%] | 1.00 |
| Lower digestive bleeding | 0/64 | 0% [0%–6%] | 1/63 | 2% [0%–8%] | 1.00 |

[a]$p < 0.05$ is considered as statistically significant.
STT: Standard triple therapy. o-BQT: Bismuth quadruple therapy. CLA: clarithromycin. CI: Confidence Interval.

***Table 3:*** **Summary of the incidence of adverse events.**

Randomized controlled trials conducted outside of Latin America have evaluated the effectiveness of different bismuth quadruple therapies compared to STT for *H. pylori* eradication. A study conducted in China compared 10-day and 14-day bismuth quadruple therapy regimens consisting of vonoprazan 20 mg twice a day, bismuth 220 mg twice a day, amoxicillin 1000 mg twice a day, and either clarithromycin 500 mg twice a day or tetracycline 500 mg four times a day, finding eradication rates of 93% and 94% respectively, with lower adverse events in the 10-day regimen.[25]

Another study in Korea compared 10-day bismuth quadruple therapy (daily doses of bismuth 300 mg, four times a day; lansoprazole 30 mg, twice a day; metronidazole 500 mg, three times a day; and tetracycline 500 mg, four times a day) or 7-day STT (lansoprazole 30 mg; amoxicillin 1000 mg; and clarithromycin 500 mg; each given three times a day), reporting higher eradication rates for bismuth quadruple therapy (74% vs. 57% in intention-to-treat analysis) but also higher discontinuation rates due to adverse events (23% vs. 9%),[26] although notably, the treatment durations were less than the recommended ideal of 14 days.

There is high variability in the bismuth quadruple therapy schemes around the world. However, the consistency in higher eradication rates for bismuth quadruple therapy across different populations underscores its effectiveness and supports its use as a first-line therapy, particularly in regions with high antibiotic resistance.

The characteristics of our trial warrant further discussion as the eradication rates were higher than

| Type of analysis | STT efficacy | | o-BQT efficacy | | Risk ratio eradication success, o-BQT vs. STT [95% CI] | Absolute risk difference the eradication rates [95% CI] | p-value |
|---|---|---|---|---|---|---|---|
| | Eradication rate (n/N) | 95% CI | Eradication rate (n/N) | 95% CI | | | |
| ITT analysis | 81.25% (52/64) | 70%–89% | 95.23% (60/63) | 86%–99% | 1.17 [1.014–1.27] | 14% [1%–20%] | 0.033 |
| PP analysis | 80.95% (51/63) | 69%–89% | 95.23% (60/63) | 86%–99% | 1.17 [1.016–1.27] | 14% [1%–21%] | 0.028 |

***Table 2:*** **Summary of efficacy results.**

expected, particularly for STT which we observed 81% eradication rate (52/64) vs. recent real-world Chilean studies with values < 70%. First, our sample presents a lower prevalence of current smoking than the general population, 14% (18/127) vs. 31%, as reported in Chile, and a reduced prevalence of diabetes mellitus, 7% (9/127) vs. 11%, in Chile.[27] Systematic reviews (SR) report that smoking increases the failure rate with Odds Ratio = 1.70 [ 1.49–1.93],[28] same with diabetic participants, who have augmented failure rates with Odds Ratio = 2.59 [1.82–3.70].[29] So, the lower prevalence of smoking and diabetes mellitus in our sample may partially explain the higher-than-expected STT eradication rates. Secondly, we found that 17% (19/127) were resistant to clarithromycin. According to a systematic review by Camargo et al., which analyzed the *H. pylori* resistance in Latin America in samples taken between 1988 and 2011, reports for Chile were 9% [2%–21%] for clarithromycin resistance, for amoxicillin 2% [0%–5%], and 31% [16%–49%] for metronidazole.[30] Previous studies in the country showed variability in clarithromycin resistance: Vallejos (2007) found 20%,[31] Otth (2011) reported 9%,[32] Parra-Sepulveda (2005–2017) observed an increase from 23% to 29%,[33] and Arenas (2019) reported 26%.[12] This indicates high variability in the country's clarithromycin resistance patterns of *H. pylori*. Indeed, the variability of clarithromycin resistance and often unknown local clarithromycin resistance prevalence further supports o-BQT as the preferred option over STT, which is consistent with North American and European guidelines.[13,14] This idea is also supported by the bivariate analysis, which in participants with clarithromycin resistance shows Risk Ratio 0.74 [0.53–0.96] (p = 0.018) in the probability of successful eradication (Table 4).

Both arms showed similar adherence. This is an important factor for eradication success. A systematic review of the effect of receiving reinforcing medication

| Variable | Eradication rate per group % (n/N) | | Risk Ratio (95% IC) | p-value[a] |
|---|---|---|---|---|
| Sex | Female | 91% (64/70) | 1.00 [Ref] | 0.31 |
| | Male | 84% (47/56) | 0.91 [0.80–1.05] | |
| Age range | 18–29 | 80% (12/15) | 1.00 [Ref] | 0.41 |
| | 30–39 | 96% (22/23) | 1.20 [0.90–1.59] | |
| | 40–49 | 81% (25/31) | 1.01 [0.73–1.39] | |
| | 50–59 | 92% (23/25) | 1.15 [0.85–1.55] | |
| | 60–69 | 87% (20/23) | 1.09 [0.79–1.49] | |
| | 70–75 | 100% (9/9) | 1.25 [0.95–1.64] | |
| Body mass index | 18.5–24.9 | 89% (24/27) | 1.00 [Ref] | 0.99 |
| | 25–29.9 | 88% (56/64) | 0.98 [0.82–1.12] | |
| | >30 | 89% (31/35) | 0.99 [0.78–1.14] | |
| Smoking | No smoker | 90% (97/108) | 1.00 [Ref] | 0.29 |
| | Smoker | 78% (14/18) | 0.87 [0.66–1.13] | |
| Diabetes Mellitus | No | 87% (102/117) | 1.00 [Ref] | 0.61 |
| | Yes | 100% (9/9) | 1.15 [1.074–1.15] | |
| High blood pressure | No | 88% (90/102) | 1.00 [Ref] | 1.00 |
| | Yes | 88% (21/24) | 0.99 [0.83–1.18] | |
| Dyslipidemia | No | 88% (104/118) | 1.00 [Ref] | 1.00 |
| | Yes | 88% (7/8) | 0.99 [0.78–1.12] | |
| Full adherence | No | 86% (24/28) | 1.00 [Ref] | 0.88 |
| | Yes | 89% (87/98) | 1.04 [0.91–1.30] | |
| Presence of any adverse reactions | No | 91% (39/43) | 1.00 [Ref] | 0.76 |
| | Yes | 87% (73/84) | 0.96 [0.87–1.13] | |
| CLA resistance | No | 92% (85/92) | 1.00 [Ref] | 0.018 |
| | Yes | 68% (13/19) | 0.74 [0.53–0.96] | |
| PPI metabolizer phenotype | Poor | 89% (74/83) | 1.06 [0.86–1.30] | |
| | Normal | 84% (16/19) | 1.00 [Ref] | 0.81 |
| | Intermediate[b] | 100% (1/1) | 0.91 [0.40–2.07] | |
| | Rapid | 80% (12/15) | 0.95 [0.69–1.31] | |
| | Ultra-rapid[b] | 100% (2/2)[b] | 1.01 [0.59–1.74] | |

PPI: Proton pump inhibitor. CLA: clarithromycin. Ref: Reference. [a]p < 0.05 is considered as statistically significant. [b]Groups with a 100% success rate (Intermediate and Ultra-rapid) required continuity correction to calculate IC and the confidence intervals.

*Table 4:* **Bivariate analysis evaluating the association between clinical covariates and H pylori eradication success.**

adherence interventions in *H. pylori* therapy found that these participants showed better medication adherence and had a higher eradication rate in intention-to-treat analysis, which values are 80% vs. 65%, Risk Ratio = 1.25 [1.12–1.31].[34]

Compared to the European Registry on *H. pylori* Management, our trial observed a higher prevalence of adverse events. This could be explained by the fact that we actively asked about adverse reactions and covered more symptoms. Reassuringly, though, none of these adverse events resulted in treatment discontinuation and were self-limited or could be managed in the primary healthcare setting, similar to other studies, including the European Registry on *H. pylori* Management.[35]

The strength of our trial lies in its robust experimental design, meticulous measurement of clinical variables, the assessment of antibiotic resistance and PPI metabolizer phenotype, and the successful execution of the follow-up process, with only one individual lost from follow-up. Our trial addresses a gap in the Latin American context where randomized controlled trials for *H. pylori* eradication schemes are limited. The survey data collected can help the scientific community better understand our populations' similar and unique characteristics to guide choices of empirical therapies. The evidence in bismuth quadruple therapy therapies in Chile is scarce, which is the first-line therapy in most international *H. pylori* guidelines, including those from the American College of Gastroenterology and Maastricht.

The distribution of CYP polymorphisms varies drastically between different ethnic groups worldwide, which has profound implications for public health and personalized medicine.[36] For example, studies in Mexico clearly illustrate the importance of population stratification. In mestizo populations, which constitute the majority of the country, the frequency of the loss-of-function allele CYP2C19*2 is in a range of 7%–11%.[37–39] While our study did not assess ethnicity, its direct measurement of CYP polymorphisms is a key strength, despite the inability to link these findings to ethnic variations in eradication probability.

Limitations exist in our trial. The reliance on a questionnaire to measure adherence, adverse reactions, and comorbidities introduces possible recall bias. The randomization process achieved imbalances in the distribution of some baseline characteristics between the groups, specifically sex (10% more men in STT), presence of diabetes mellitus (8% more in o-BQT), and smoking status (6% more in o-BQT). However, the smoking status, diabetes mellitus, and sex did not seem to be significant variables in the bivariate analysis Table 4. Consequently, the assigned treatment seems to be the most crucial variable in the probability of success in *H. pylori* eradication.

Additionally, the PPI metabolizer phenotype and antibiotic resistance to clarithromycin were similar in both groups within the trial sample, which we believe allows for a valid comparison between the two treatment regimens. When combined with therapeutic adherence and the occurrence of adverse reactions, these factors offer a thorough assessment of the elements associated with eradication success. The measurement of PPI metabolizer phenotype and resistance to clarithromycin supports the conclusion that the treatment scheme employed is the key predictor of effectiveness.

In clinical terms, the o-BQT eradication rate surpasses the optimal threshold of 90%, as recommended by The Maastricht Consensus for *H. pylori* management.[13] The success of the o-BQT scheme in this trial relies on the full optimization for our local context. The election of amoxicillin is because it has shown low resistance over decades of use, and metronidazole because at 1500 mg/day, it overcomes the resistance of *H. pylori* strain, along with the use of bismuth.[30,40]

It is important to highlight that even though we used a high dose of PPI, we observed a safe profile, with almost the same frequency of adverse reactions in the o-BQT scheme compared to STT, which used omeprazole 20 mg twice a day. Patient-reported adverse effects were common (41%), but in line with prior literature; importantly, this did not appear to differentially impact treatment adherence, particularly with o-BQT.[41] Abdominal distention was the only symptom that had a statistically significant difference between the two groups, with a higher frequency among patients in the o-BQT vs. STT group with 30% (19/63) [20%–42%] vs. 13% (8/64) [7%–23%], p = 0.03). This was not considered severe in any patients, but patients should be counseled regarding this and other anticipated side effects to optimize treatment adherence.

For clinicians caring for subjects with *H. pylori* infection, especially in zones with known high resistance to clarithromycin (>15%), this fully optimized o-BQT therapy is a reliable and safe option as a first-line empiric eradication therapy. STT is not a good option as an empiric therapy unless susceptibility testing to clarithromycin is performed before use.

In conclusion, our findings support the idea that our full *optimized bismuth quadruple therapy* scheme consisting of esomeprazole 40 mg three times a day, amoxicillin 1 gr three times a day, metronidazole 500 mg three times a day, and bismuth subsalicylate 369 mg three times a day for 14 days represents the optimal as first-line empirical therapy for eradication of *H. pylori* infection in Chile and similar countries, as a reliable option, with a similar safety profile and no significant differences in the incidence of adverse reactions with the STT. These results underscore the importance of randomized controlled trials data in

informing evidence-based clinical practice recommendations and ensuring that insurance covers the most effective, safe treatments.

#### Contributors

Conceived and designed the study: P.A.M-J., R.J.H., S.C.S., A.R.P.; Recruited patients and performed Data collection: P.A.M-J., G.L., E.F-L., J.C., S.M., O.C., D.R., A.E., J.I.V., A.R.P.; Performed laboratory analysis: C.S., I.B., C.S., N.M.V., L.C., L.Q.; Analyzed the data and have full Access of the data: P.A.M-J., .E.F-L., D.R., I.A.W, A.R.P.; Wrote the manuscript: P.A.M-J., E.F-L., M.P., D.R., R.J.H, S.C.S. A.R.P.; Reviewed and approval of submetted manuscript: G.L., E.F-L., M.P., P.V., J.C., S.M., O.C., D.R., A.E., J.I.V., I.A.W., P.H, C.S., I.B., L.C., L.Q., F.M., R.J.H., S.C.S., A.R.P. Responsible for the decision to submit the manuscript: P.A.M-J, R.J.H., S.C.S., A.R.P.

#### Data sharing statement

Individual participant data will not be available. The trial protocol is available in the Supplemental Material.

#### Declaration of interests

This work is part of an Epidemiology PhD thesis at Pontificia Universidad Católica de Chile on *H. pylori* eradication made by Patricio Medel-Jara, titled "Clinical Epidemiology: Optimization of eradication treatment for *H. pylori* in Latin America and Chile" (original name Epidemiología Clínica: Optimización del tratamiento de erradicación para el *H. pylori* en Latinoamérica y Chile). Dr. Shailja Sha had consulting fees from Phantom Pharmaceuticals and RedHill Biopharma, not related with this study and Dr. Arnoldo Riquelme received the UBT test from Meridian and Bismuth Subsalicylate with placebos for the study and mentioned in the acknowledgements. The authors declare there are no other potential conflicts of interest.

#### Acknowledgements

The funding of this project is by Public policy: "Strategies for Gastric Cancer Prevention in Chile" UC (AR); FONDECYT 1230504 (AR) "Role of the genomic and microbiome profile in gastric carcinogenesis: prospective endoscopic follow-up"; ANID FONDAP 152220002 (AR) "Center for Cancer Prevention and Control (CECAN)" and LEGACy "CeLac and European consortium for a personalized medicine approach to Gastric Cancer"; no 825832 of the Horizon 2020 programme of European Union (AR); ANID FONDAP 15130011 (IAW) "ACCDiS: Advanced Center for Chronic Diseases". To Maver Laboratories for providing Gastroaliv and placebo tablets and to Meridian Bioscience for providing the urea breath test.

#### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2025.101312.

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