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Use of a combination formulation of bismuth, metronidazole and tetracycline with omeprazole as a rescue therapy for eradication of *Helicobacter pylori*

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SUMMARY

Background
Helicobacter pylori infection occurs in children and adults worldwide. Standard triple therapy of omeprazole, amoxicillin and clarithromycin (OAC) may not be optimal.

Aim
To evaluate quadruple therapy with bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride, given with omeprazole in *H. pylori* infected subjects who failed previous OAC eradication therapy.

Methods
This was a multicenter, open-label, single-arm, multinational study. *Helicobacter pylori*-positive subjects who had failed ≥1 previous course of OAC therapy with or without up to three supplemental treatments in the previous year. Subjects were treated for 10 days with a combination formulation containing bismuth subcitrate potassium 140 mg, tetracycline hydrochloride 125 mg, and metronidazole 125 mg, three capsules four times daily (q.d.s.), and omeprazole 20 mg twice daily (b.d.). The primary endpoint was *H. pylori* eradication rate defined as one negative ^{13}C-urea breath test ≥28 days post-treatment.

Results
Helicobacter pylori eradication rates ranged from 93.2% to 93.8% in the intent-to-treat population (n = 49), and from 94.7% to 95.0% in the PP population (n = 40). No clinically meaningful differences were observed when analysed by country. Metronidazole resistance was observed in 16/49 (32.7%) subjects and clarithromycin resistance in 31/49 (63.3%) subjects. Thirty-three subjects (67.3%) reported 87 adverse events, and only one (2%) discontinued the study for an adverse event.

Conclusions
A quadruple regimen of bismuth, metronidazole and tetracycline plus omeprazole produces a high eradication rate in subjects previously failing *H. pylori* eradication regimens. This bismuth-based regimen offers an effective option as rescue therapy.

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INTRODUCTION

Helicobacter pylori infection is common in the gastrointestinal (GI) tract and eradication is performed for a variety of specific indications. *Helicobacter pylori* occurs in over 50% of the global population,[1] and may lead to significant clinical manifestations including peptic ulcer disease (PUD) and gastric carcinoma.[1, 2] Consensus statements agree that *H. pylori* infection should be eradicated whenever diagnosed and in several specific associated clinical conditions.[3] Primary treatment is eradication of the infection with oral administration of antibiotic combinations shown to be active against *H. pylori*, which are usually combined with a proton pump inhibitor (PPI).[1]

A major challenge with managing *H. pylori* is that resistance rates to antibiotics vary in different countries and even within different regions of the same country.[4, 5] Treatment failure, recurrence and re-infection most often arise because of antibiotic resistance or poor compliance with therapy.[6, 7] High rates of antibiotic resistance approaching and exceeding 30% in some regions of the world pose a challenge when selecting the most effective regimen for initial therapy.[1, 5, 8] Because of high rates of clarithromycin resistance, triple therapy with omeprazole, amoxicillin and clarithromycin (OAC) is inappropriate, when the local clarithromycin resistance rates exceed 20%.[1, 3] Treatment guidelines recommend the use of alternative antibiotics for local clarithromycin resistance rates >30%.[1, 3]

Quadruple therapy with bismuth subcitrate, metronidazole and tetracycline given together with a PPI has demonstrated eradication rates exceeding 80–90% in randomized controlled trials as primary therapy and seems to be highly effective even in strains which are resistant to metronidazole.[9, 10] Quadruple therapy is thus currently recommended in *H. pylori* treatment guidelines as an alternative to OAC regimens.[1, 11, 12] In the European Consensus Report, bismuth-based quadruple therapy is recommended first line in regions with high clarithromycin resistance.[3] However, quadruple bismuth-based therapy has not been well studied in subjects who have failed previous therapy. The purpose of this study was to evaluate the *H. pylori* eradication rate following quadruple therapy with a combination formulation containing in one capsule bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride (Pylera®, Aptalis Pharma, Bridgewater, NJ, USA) administered four times daily, given with omeprazole twice daily in *H. pylori* infected subjects, who had failed at least one previous course of OAC eradication therapy. This combination formulation is intended to simplify treatment administration of multiple antibiotics and to improve treatment compliance.

METHODS

This was a Phase 3b, open-label, single-arm, clinical trial conducted at 11 clinical sites in France, Germany, Italy, and Spain between March 2012 and January 2013. Subjects were recruited from those attending gastroenterology clinics at each study site. The study was conducted in accordance to the principles of the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practices. The study protocol and informed consent documents were approved by an Institutional Review Board for each study site, and written informed consent was obtained from each subject prior to any study procedures.

Subject selection

Men or nonpregnant, nonnursing women at least 18 years of age were eligible, if they were positive for *H. pylori* using a carbon-13 urea breath test (^{13}C-UBT) and a Rapid Urease Test (RUT). Subjects must have had a documented failure with at least one prior course of OAC treatment with or without one to three supplemental treatments. Subjects also were required to have upper GI symptoms. Women of child-bearing age were required to use a medically acceptable form of birth control for the duration of the study.

Subjects were excluded for any previous use of a bismuth, metronidazole and tetracycline combination regimen for *H. pylori* eradication. Subjects also were excluded for previous surgery of the upper GI tract, history of Zollinger–Ellison Syndrome, Barrett's oesophagus or high grade dysplasia, dysphagia or vomiting, continuous use of anti-ulcer drugs or a PPI within 2 weeks of screening, chronic use of nonsteroidal anti-inflammatory drugs, requirement for anti-coagulants or platelet aggregation inhibitors, use of systemic antibiotics within 30 days, regular use of bismuth compounds within 30 days or known sensitivity to any of the study drugs. Subjects with any medical condition that could interfere with the conduct of the study were excluded.

Study procedures

During a Screening Phase lasting up to 30 days prior to the start of study treatment, a complete medical/surgical history, physical examination and vital signs (heart rate,

blood pressure, respiratory rate and body temperature) as well as clinical laboratory tests and a serum pregnancy test were obtained. Subjects underwent upper GI endoscopy to obtain gastric biopsies, and a ^{13}C-UBT was obtained. The endoscopy was performed to obtain three biopsies: two from the antrum and one from the body of the stomach. One antrum biopsy was used on-site for a RUT, and the remaining two biopsies were used for culture to determine the presence of *H. pylori*, to assess antibiotic resistance by polymerase chain reaction (PCR), and to determine minimum inhibitory concentrations (MIC) for antibiotics. The ^{13}C-UBT was analysed by a central laboratory (INFAI, Koln, Germany). Subjects fasted for at least 6 h prior to the test. Subjects were asked to blow into a tube, then to drink a test meal (^{13}C-labelled urea solution) and blow again into the tube 30 min after drinking the solution. Confirmation of the presence of *H. pylori* was assessed by RUT.

At the beginning of a 10-day Treatment Phase, vital signs were obtained from each subject, and study medication was dispensed. During the End of Treatment Phase from Day 11–Day 14, clinical laboratory tests and vital signs were obtained. At the End of Study (EOS) Phase or between Day 39 and Day 56, a physical examination, vital signs, clinical laboratory tests, serum pregnancy test and ^{13}C-UBT were repeated.

Study treatments

Study drug consisted of a combination formulation containing bismuth subcitrate potassium 140 mg (equivalent to bismuth oxide 40 mg), metronidazole 125 mg and tetracycline hydrochloride 125 mg in each capsule (Pylera® Aptalis Pharma, Bridgewater, NJ, USA). Subjects received three capsules of bismuth, metronidazole and tetracycline four times daily delivering a total daily dose of bismuth 480 mg, tetracycline hydrochloride 1500 mg, metronidazole 1500 mg, after meals and at bedtime after a snack. In addition, subjects received omeprazole 20 mg twice daily taken after breakfast and evening meals together with the bismuth, metronidazole and tetracycline capsules. Capsules were swallowed whole with a full glass of water (250 mL). Ingestion of adequate amounts of fluid was recommended to reduce the risk of oesophageal irritation and ulcers by tetracycline. Subjects were instructed not to take study drug with dairy products (such as milk or yogurt or drinks with added calcium) or with antacids. Subjects were also allowed to take antacids as rescue medication for relief of heartburn. Rescue medication consisted of 200 mg of dried aluminium hydroxide gel, 200 mg of magnesium hydroxide, and 25 mg of simethicone (Maalox® Plus, Sanofi Aventis, Paris, France), which could be taken as two tablets as needed up to a maximum of four times a day.

Study analysis

The primary efficacy endpoint was the *H. pylori* eradication rate, where eradication was defined as one negative ^{13}C-UBT performed at least 28 days post-treatment. Mean, median, standard deviation, minimum and maximum were calculated for continuous data and frequency counts and percentages for categorical data. Exact 95% confidence intervals (CIs) about the eradication rates, based on the binomial distribution, were calculated. Data were analysed for the intent-to-treat (ITT), which included all enrolled subjects who took at least one dose of study medication, and the per-protocol (PP) population, which included all ITT subjects who completed the study without any events that could potentially bias the study outcome.

RESULTS

Sixty-four subjects were screened, and 49 were included in the ITT population. One subject discontinued the study for an adverse event. Nine were excluded from the PP population for major protocol deviations including lack of compliance, use of prohibited concomitant medications, abnormal laboratory results and failure to meet inclusion/exclusion criteria. Baseline demographical characteristics are shown in Table 1. At screening, the PCR test was positive in 96% (ITT) to 100% (PP) of subjects, and two-thirds of subjects demonstrated *H. pylori* resistance to at least one of clarithromycin, metronidazole or a fluoroquinolone (Table 1). Metronidazole resistance was observed in 16/49 (32.7%) subjects and clarithromycin resistance was observed in 31/49 (63.3%) subjects. At screening, the ^{13}C-UBT and the RUT were positive for *H. pylori* in all 49 subjects. All 49 subjects had a prior history of using medications to treat *H. pylori* most often clarithromycin, amoxicillin and PPIs (Figure 1). In the ITT population, *H. pylori* resistance to at least one antibiotic was highest in Germany [9/12 (75.0%)] and similar in France [8/13 (61.5%)] and Spain [15/23 (65.2%)]. France had the highest *H. pylori* resistance to clarithromycin and metronidazole [7/13 (53.8%)].

Efficacy

Mean treatment compliance with study drug was 98% for the bismuth, metronidazole, tetracycline component and 99% for the omeprazole component of the treatment regimen. In the ITT population, *H. pylori* eradication

Table 1 | Baseline demographical characteristics

Characteristic	ITT population (n = 49)	PP population (n = 40)
Age (years)* [range]	45.3 (13.0) [22–74]	44.2 (13.7) [22–74]
Male, *n* (%)	24 (49.0)	22 (55.0)
Body mass index (kg/m^2)* [range]	26.0 (4.1) [20.3–37.5]	26.1 (4.4) [20.3–37.5]
Months since infected with *Helicobacter pylori** [range]	6.3 (3.6) [2–17]	6.0 (3.7) [2–17]
Presence or past history of ulcer, *n* (%)	7 (14.3)	7 (17.5)
Screening PCR test positive, *n* (%)	47 (95.9)	40 (100.0)
Helicobacter pylori resistant to: *n* (%)		
At least one antibiotic (below)	33 (67.3)	27 (67.5)
Clarithromycin (MIC ≥1 μg/mL)	31 (63.3)	26 (65.0)
Fluoroquinolone (MIC ≥1 μg/mL)	5 (10.2)	3 (7.5)
Metronidazole (MIC >8 μg/mL)	16 (32.7)	13 (32.5)
All three antibiotics	3 (6.1)	2 (5.0)

* Mean (standard deviation); PCR, polymerase chain reaction.

ranged from 93.2% to 93.8%, regardless of the definition of eradication (Table 2). A similar finding was observed in the PP population where eradication rates ranged from 94.7% to 95.0%. No clinically meaningful differences in the eradication rates were observed when analysed by country for either the ITT or PP population (Figure 1). The cure rate was 93.9% (31 of 33 subjects) and in metronidazole-sensitive subjects and 93.7% (15 of 16 subjects) in metronidazole-resistant subjects.

Three subjects in the ITT Population were positive for *H. pylori* at the EOS visit. Two subjects did not exhibit resistance to clarithromycin (MIC >1 μg/mL), metronidazole (MIC >8 μg/mL) or fluoroquinolones. The third subject was resistant to metronidazole. None of these subjects had a history or presence of peptic ulcer, and all three had received previous antibiotic treatment for *H. pylori* with concomitant PPI.

Tolerability

Of 49 subjects included in the safety population, 33 (67.3%) reported 87 individual treatment-emergent adverse events (TEAEs) (Table 3). One subject discontinued the study for severe headache, moderate back pain and moderate dyspepsia that occurred after 1.5 days of study drug. GI TEAEs were the most commonly reported, occurring in 28 (57.1%) subjects including dyspepsia, discoloured faeces, diarrhoea, abdominal pain and discomfort, nausea, and vomiting. Central nervous system TEAEs [11 (22.4%)] include dysgeusia and headache. Five (10.2%) subjects reported severe TEAEs including dyspepsia, nausea, headache and loss of libido.

No clinically significant changes in physical examination findings or vital signs occurred. No clinically significant changes in laboratory tests were noted.

DISCUSSION

In this open-label, uncontrolled trial of subjects who had failed at least one course of OAC treatment, the *H. pylori* eradication rate was 93% in the ITT population and 95%

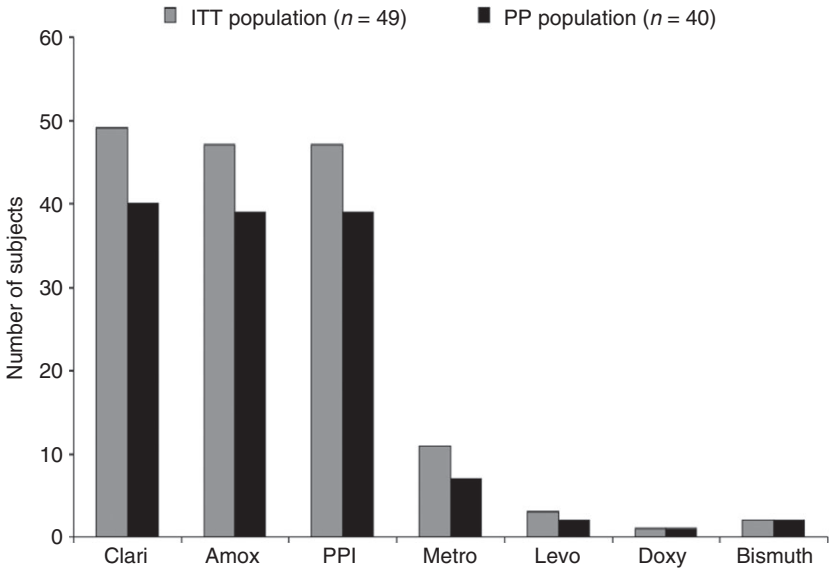

Figure 1 | Prior medications used to treat *Helicobacter pylori* in the ITT and PP populations.

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Table 2 | *Helicobacter pylori* eradication rate in ITT and PP populations

	ITT population (n = 49)	PP population (n = 40)
Number with ^{13}C-UBT 28–56 days following the last day of treatment	44	38
Number (%) eradicated	41 (93.2)	36 (94.7)
95% confidence interval	81.3, 98.6	82.3, 99.4
Number with ^{13}C-UBT ≥28 days following the last day of treatment	47	40
Number (%) eradicated	44 (93.6)	38 (95.0)
95% confidence interval	82.5, 98.7	83.1, 99.4
Number with ^{13}C-UBT following the last day of treatment	48	40
Number (%) eradicated	45 (93.8)	38 (95.0)
95% confidence interval	82.8, 98.7	83.1, 99.4

^{13}C-UBT, 13C-urea breath test.

Table 3 | Incidence of treatment-emergent adverse events occurring in at least 4% of subjects

Event	Number (%) of subjects (n = 49)
Any event	33 (67.3)
Dyspepsia	12 (24.5)
Discoloured faeces	9 (18.4)
Diarrhoea	6 (12.2)
Dysgeusia	6 (12.2)
Abdominal discomfort	4 (8.2)
Headache	4 (8.2)
Nausea	4 (8.2)
Decreased appetite	3 (6.1)
Dizziness	3 (6.1)
Vomiting	3 (6.1)
Abdominal pain, upper	2 (4.1)
Back pain	2 (4.1)
Fatigue	2 (4.1)
Oral herpes	2 (4.1)
Transaminases increased	2 (4.1)

in the PP population with bismuth-based quadruple therapy given for 10 days. No difference in eradication rates was found when results were analysed across countries enrolling subjects. Mean compliance with the quadruple regimen was >95%, which is consistent with results previously reported with this formulation and with bismuth-based quadruple therapy.[10, 13, 14]

The tolerability profile of this bismuth-based quadruple regimen was consistent with previous experience[9, 10] and consisted mostly of GI side effects. Nervous system symptoms occurred in 22.4% of subjects and consisted of transient dysgeusia, headache and dizziness. Only five severe TEAEs and no serious adverse events were observed, and only one subject discontinued the study for a severe adverse event (headache).

A concern with the use of bismuth-based regimens arose from the experience in France and Australia in the 1970s, where high doses of bismuth salts used over weeks to months or longer for common GI complaints were associated with neurotoxicity including bismuth-associated encephalopathy and fatalities.[15–18] Other than headache and dizziness in less than 10% of subjects, we found no evidence of neurological symptoms in our study, which is consistent with findings from a meta-analysis of safety with the use of bismuth salts for *H. pylori* eradication.[19]

Bismuth-based triple therapy was used for *H. pylori* eradication for many years, but in the face of increasing anti-microbial resistance, a PPI was added to the regimen with a marked increase in eradication rates even in the presence of resistance.[20] Meta-analyses and systematic reviews have reported that bismuth-based quadruple regimens are at least as effective as other regimens for initial treatment and eradication of *H. pylori* infection.[13, 14] Current treatment guidelines recommend bismuth-based quadruple regimens as a first line therapy for *H. pylori*.[1, 3, 11] However, use of a bismuth-based regimen for rescue therapy in subjects who have failed one or more courses of antibiotic therapy has been poorly studied.

The majority of published literature on bismuth-based quadruple therapy as rescue therapy is from the Asia-Pacific region, where *H. pylori* resistance rates to many antibiotics are high, and consequently, eradication rates are low.[21] A bismuth-based quadruple regimen of esomeprazole, bismuth, metronidazole and tetracycline vs. esomeprazole, moxifloxacin and amoxicillin were compared in randomized controlled trial in subjects who had failed first line therapy.[22] However, the primary outcome was re-infection rate at 1 year rather than eradication rate. Wang and colleagues[23] compared two quadruple regimens for rescue therapy (esomeprazole, bismuth, amoxicillin, doxycycline vs. esomeprazole, bismuth, metronidazole, tetracycline) in 85 subjects treated for 10 days, but eradication rates were less than 75% for both regimens. Lee and colleagues[24] compared 1 week and 2 week regimens of a bismuth-based quadruple therapy (bismuth, metronidazole, tetracycline and esomeprazole) and reported eradication rates of 77% and 93%,

respectively. A prospective study in Spain found that a bismuth-containing quadruple regimen was an effective third-line therapy after two previous treatment failures.[25] It is important to note that these studies were performed with a bismuth-based quadruple regimen that differs in the bismuth salt and the antibiotic dosages and composition from the formulation used in this study.

It is not known whether a 14-day regimen of bismuth quadruple therapy as rescue therapy may further improve eradication rates. Data for treatment as primary therapy are ambiguous. An open-label pilot study of 47 Hispanic subjects reported a per-protocol 97% eradication rate overall and 100% in metronidazole-resistant strains.[26] However, a randomized study of 417 subjects found no difference in PP or ITT eradication rates between twice daily 10-day and 14-day regimens.[27]

Limitations of this study are its open-label design with a single treatment arm and its relatively small sample size. The strength of the present study is that antibiotic sensitivity was assessed prior to treatment, which confirmed the high rate of clarithromycin resistance and the absence of an impact from metronidazole resistance on treatment efficacy. Thus, results from this study indicate that this combination formulation of quadruple therapy consisting of bismuth, metronidazole and tetracycline plus omeprazole provides high *H. pylori* eradication rates in subjects previously failing a clarithromycin-based regimen. These results provide evidence for a bismuth-based quadruple regimen as an effective option as rescue therapy for *H. pylori* eradication.

AUTHORSHIP

Guarantor of the article: Peter Malfertheiner.

Author contributions: Ruth Thieroff-Ekerdt designed the research study, supervised data collection and data analysis, and contributed to writing of the manuscript. Peter Malfertheiner and Jean-Charles Delchier contributed to study design, patient enrolment, had full access to all the study data and contributed to writing the manuscript. All authors approved the final version of the manuscript.

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