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ORIGINAL RESEARCH

Effect of MMX® mesalamine coadministration on the pharmacokinetics of amoxicillin, ciprofloxacin XR, metronidazole, and sulfamethoxazole: results from four randomized clinical trials

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Background: MMX® mesalamine is a once daily oral 5-aminosalicylic acid formulation, effective in induction and maintenance of ulcerative colitis remission. Patients on long-term mesalamine maintenance may occasionally require concomitant antibiotic treatment for unrelated infections.

Aim: To evaluate the potential for pharmacokinetic interactions between MMX mesalamine and amoxicillin, ciprofloxacin extended release (XR), metronidazole, or sulfamethoxazole in four open-label, randomized, placebo-controlled, two-period crossover studies.

Methods: In all four studies, healthy adults received placebo once daily or MMX mesalamine 4.8 g once daily on days 1–4 in one of two treatment sequences. In studies 1 and 2, subjects also received a single dose of amoxicillin 500 mg (N=62) or ciprofloxacin XR 500 mg (N=30) on day 4. In studies 3 and 4, subjects received metronidazole 750 mg twice daily on days 1–3 and once on day 4 (N=30); or sulfamethoxazole 800 mg/trimethoprim 160 mg twice daily on days 1–3 and once on day 4 (N=44).

Results: MMX mesalamine had no significant effects on systemic exposure to amoxicillin, ciprofloxacin, or metronidazole; the 90% confidence intervals (CIs) around the geometric mean ratios (antibiotic + MMX mesalamine: antibiotic + placebo) for maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve (AUC) fell within the predefined equivalence range (0.80–1.25). Sulfamethoxazole exposure increased by a statistically significant amount when coadministered with MMX mesalamine; however, increased exposure (by 12% in C_{max} at steady state; by 15% in AUC at steady state) was not considered clinically significant, as the 90% CIs for each point estimate fell entirely within the predefined equivalence range. Adverse events in all studies were generally mild.

Conclusion: MMX mesalamine may be coadministered with amoxicillin, ciprofloxacin, metronidazole, or sulfamethoxazole, without affecting pharmacokinetics or safety of these antibiotics.

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Keywords: ulcerative colitis, pharmacokinetics, safety

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease affecting more than one million people in Europe and the United States.[1–3] UC is characterized by a diverse range of relapsing–remitting gastrointestinal and systemic symptoms, including the characteristic clinical symptom of bloody diarrhea that frequently presents with rectal

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urgency and tenesmus.[4] In UC management, the primary goals are induction and maintenance of disease remission in order to improve the patient's health and quality of life, reduce the need for long-term corticosteroids, and minimize cancer risk.[4] The anti-inflammatory agent 5-aminosalicylic acid (5-ASA) is the standard first-line therapy for active mild-to-moderate UC.[4] MMX Multi Matrix System® (MMX®; MMX Multi Matrix System®, and MMX® are registered trademarks of Cosmo Technologies Ltd, Wicklow, Ireland) mesalamine is a once daily oral formulation of 5-ASA that has shown efficacy in the induction and maintenance of remission in UC.[5–8]

Given that UC is a lifelong condition, patients with UC frequently require maintenance therapy for many years. Thus, it is likely that UC patients on MMX mesalamine will require concomitant treatment with other medications, including antibiotics for management of infections, at some point during maintenance therapy. A study that assessed health care resource utilization in inflammatory bowel disease, including reports on antibiotic use among patients, demonstrated that approximately 45% of patients with UC had received antibiotics within the last 18 months, and 4.5% within the previous 2 weeks.[9] Thus, it is critical to evaluate potential pharmacokinetic drug–drug interactions that may result in a change in the metabolism, absorption, distribution, or elimination of commonly administered antibiotics.

To put these drug interaction studies in context, it should first be noted that these studies were originally conceived in support of a program to develop MMX mesalamine for prevention of recurrence of diverticulitis. Acute diverticulitis is generally associated with intra-abdominal infections composed of mixed aerobic and anaerobic bacteria.[10] The standard of care involves administration of broad-spectrum antibiotics, which treat the acute flare but do not necessarily preclude recurrence in the future, possibly resulting in a need for surgical intervention. Preliminary reports in the literature have suggested that chronic administration of MMX mesalamine following treatment of acute diverticulitis might prevent or delay recurrence of the condition.[11–16] To formally assess this possibility, two clinical trials were conducted to evaluate the efficacy and safety of MMX mesalamine in the prevention of recurrence of diverticulitis (PREVENT1 [NCT00545740][17] and PREVENT2 [NCT00545103][18]). Data from the PREVENT studies will be published separately. Drug interaction studies were also conducted to provide assurance that MMX mesalamine could be safely administered during or immediately following the acute treatment of diverticulitis. Antibiotics for study were selected based on being either most commonly prescribed in diverticulitis or at risk of interaction because of shared metabolic or elimination pathways. The antibiotics studied with respect to drug interactions are also used for treatment of common infections likely to be experienced by patients with UC. Hence, the outcome of these drug interaction studies is considered of value to gastroenterologists prescribing mesalamines for this population.

Three antibiotics (amoxicillin, ciprofloxacin, and metronidazole) were selected for evaluation because they are the most widely used antibiotics to treat acute diverticulitis[19–21] and are representative of three major classes of broad-spectrum antibiotics (ie, penicillins, fluoroquinolones, and nitroimidazoles, respectively). A fourth antibiotic (sulfamethoxazole) was selected on the basis of sharing a major metabolic pathway with mesalamine.

Amoxicillin and ciprofloxacin are eliminated predominantly by excretion of unchanged drug in urine, with approximately 40% and 30% of doses, respectively, being subject to oxidative metabolism.[22–27] Metronidazole is mainly oxidatively metabolized by cytochrome P450 to hydroxymetronidazole,[28] with CYP2A6 as the principal enzyme involved.[29] Sulfamethoxazole is conjugated in the liver by N-acetyltransferase (NAT)-1 and NAT-2[30,31] to its N4-acetyl metabolite.[32] MMX mesalamine is not subject to oxidative metabolism, and in human microsomal incubations (IC_{50} [half maximal inhibitory concentration] >100 μM), it does not appear to inhibit cytochrome P450 activity.[33] Similar to sulfamethoxazole, mesalamine is primarily acetylated to N-acetyl-mesalamine[28] by NAT-1.[34,35] Based on consideration of routes of biotransformation of MMX mesalamine and of the selected antibiotics, it was anticipated that MMX mesalamine would not influence the pharmacokinetics of amoxicillin, ciprofloxacin, or metronidazole. However, it was plausible that there would be an interaction between MMX mesalamine and sulfamethoxazole. Therefore, in this context, the potential for pharmacokinetic interactions of these antibiotics with MMX mesalamine was explored in four separate studies that evaluated the pharmacokinetics and safety of amoxicillin, ciprofloxacin extended release (XR), metronidazole, and sulfamethoxazole (administered as a combination of sulfamethoxazole/trimethoprim) after each antibiotic was coadministered with placebo or with MMX mesalamine.

Materials and methods

Eligibility criteria and study design

Subjects in all studies provided written informed consent and were tested at a single site (PRA International, Lenexa, KS,

USA). Eligible subjects for all studies were healthy males or nonlactating, nonpregnant females aged 18–55 years. Subjects were required to have a body mass index of 18.5–30.0 kg/m^2 and hemoglobin levels ≥12 g/dL. Key exclusion criteria included: nicotine use (unless last use was ≥30 days prior to screening); history of disease affecting the colon, including gastrointestinal disease, peptic ulceration, gastrointestinal bleeding, celiac disease, lactose intolerance, UC, Crohn's disease, or irritable bowel syndrome; physician-diagnosed chronic constipation; renal disease or impairment; asthma associated with 5-ASA use; and pancreatitis.

All studies were conducted in accordance with the International Conference on Harmonization of Good Clinical Practice[36] guidelines and the principles of the Declaration of Helsinki. Study protocols and informed consent documents were reviewed and approved by the Institutional Review Board (ClinicalTrials.gov registration numbers: NCT01442688[37] [study 1], NCT01402947[38] [study 2], NCT01418365[39] [study 3], and NCT01469637[40] [study 4]).

All studies were open-label, randomized, placebo-controlled, two-period crossover, Phase 1 trials. The primary objective of each study was to examine the pharmacokinetics of amoxicillin, ciprofloxacin XR, metronidazole, or sulfamethoxazole when administered alone (with placebo) or in combination with MMX mesalamine. The secondary objective was to evaluate safety.

A four-digit randomization number was allocated to each eligible subject immediately prior to dosing; the randomization schedule was produced and held by PRA International (Raleigh, NC, USA). Subjects in each study were randomized 1:1 to treatment sequence AB or BA, where treatment A was orally administered MMX mesalamine placebo tablets (primarily composed of bibasic calcium phosphate bihydrate, microcrystalline cellulose, and mannitol; hereafter referred to as "placebo") plus antibiotic, and treatment B was orally administered MMX mesalamine tablets plus antibiotic. In all studies, MMX mesalamine was administered once daily for 4 days. Amoxicillin and ciprofloxacin XR were administered as single doses, because they do not accumulate on repeated dosing, whereas metronidazole and sulfamethoxazole were administered as repeated doses every 12 hours, as they do accumulate. Subjects were required to fast overnight (approximately 10 hours) prior to morning dose administration on all days, until 4 hours post-dose.

Study 1

- Treatment A consisted of a placebo tablet administered orally once daily on days 1–4 plus a single oral dose of amoxicillin (500 mg capsule) on day 4.
- Treatment B consisted of MMX mesalamine (4.8 g tablet) administered orally once daily on days 1–4 plus a single oral dose of amoxicillin (500 mg capsule) on day 4.

Study 2

- Treatment A consisted of a placebo tablet administered orally once daily on days 1–4 plus a single oral dose of ciprofloxacin XR (500 mg tablet) on day 4.
- Treatment B consisted of MMX mesalamine (4.8 g tablet) given orally once daily on days 1–4 plus a single oral dose of ciprofloxacin XR (500 mg tablet) on day 4.

Study 3

- Treatment A consisted of a placebo tablet administered orally once daily on days 1–4 plus oral metronidazole (750 mg tablet) twice daily on days 1–3 and a single dose of metronidazole (750 mg tablet) on day 4.
- Treatment B consisted of MMX mesalamine (4.8 g tablet) administered orally once daily on days 1–4 plus oral metronidazole (750 mg tablet) twice daily on days 1–3 and a single dose of metronidazole (750 mg tablet) on day 4.

Study 4

- Treatment A consisted of a placebo tablet administered orally once daily on days 1–4 plus oral sulfamethoxazole 800 mg/trimethoprim 160 mg tablets twice daily on days 1–3 and a single dose of sulfamethoxazole 800 mg/trimethoprim 160 mg tablets on day 4.
- Treatment B consisted of MMX mesalamine (4.8 g tablet) administered orally once daily on days 1–4 plus oral sulfamethoxazole 800 mg/trimethoprim 160 mg tablets twice daily on days 1–3 and a single dose of sulfamethoxazole 800 mg/trimethoprim 160 mg tablets on day 4.

In each study, subjects were screened within 28 days prior to the first dose of the study, with a planned treatment period duration of 17 days (including a 7-day washout period that occurred between treatment periods) and a planned follow-up duration of 7 days.

Pharmacokinetic evaluations and analyses

For study 1 (amoxicillin), 2 mL blood samples were drawn pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 4, 6, 8, 10, 12, 13, 14, 18, 20, 22, and 24 hours post-dose on day 4 of each treatment period. For study 2 (ciprofloxacin XR), 3 mL blood samples were collected pre-dose and at 0.5, 2, 3, 4, 5, 5.5, 6, 8, 10, 12, 13, 14, 16, 18, 20, 22, and 24 hours post-dose on day 4 of each treatment period. For subjects in studies 3 and 4

(metronidazole and sulfamethoxazole, respectively), two 2 mL blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 13, 14, 16, 18, 20, 22, and 24 hours post-dose on day 4 of each treatment period. All sampling schedules took account of the published pharmacokinetic profiles of each of the antibiotics under investigation.[41–47]

Plasma samples were analyzed for amoxicillin in study 1, ciprofloxacin in study 2, metronidazole and its active metabolite hydroxymetronidazole in study 3, and sulfamethoxazole in study 4 using validated assays employing protein precipitation followed by liquid chromatography with tandem mass spectrometry (York Bioanalytical Solutions, North York, UK). The analytical method was linear for each drug, and the lower limit of quantification was determined using the standard approach detailed in the US Food and Drug Administration (FDA) bioanalytical guidelines,[48] which require that the accuracy and precision is determined at the lower limit of quantification using at least five replicate samples, with the reported results falling within 15% of the coefficient of variation (CV). The linear ranges for each of the antibiotics were 100–20,000 ng/mL for amoxicillin, 5–5,000 ng/mL for ciprofloxacin, 500–30,000 ng/mL for metronidazole, 100–10,000 ng/mL for hydroxymetronidazole, and 1–100 µg/mL for sulfamethoxazole.

Quality control (QC) samples were prepared in control human plasma at three concentration levels (low, medium, and high) for studies 1, 2, and 4 (amoxicillin, 300 ng/mL, 1,500 ng/mL, and 15,000 ng/mL; ciprofloxacin, 15 ng/mL, 100 ng/mL, and 4,000 ng/mL; and sulfamethoxazole, 3, 10, and 75 µg/mL). For study 3, QC samples were prepared at four concentration levels each (low, medium, high, and highest) for metronidazole (1.5, 10, 24, and 150 µg/mL) and hydroxymetronidazole (0.3, 1, 7.5, and 50 µg/mL). All study QC samples were included alongside incurred samples in each batch of analyses to assess accuracy and precision of the assays according to FDA guidance.[49] Sample dilution was verified by analysis of dilution QC samples in each run. Incurred sample reproducibility was also assessed for amoxicillin, ciprofloxacin, metronidazole, hydroxymetronidazole, and sulfamethoxazole in order to ensure that the reproducibility met the predefined FDA acceptance criteria.[50] The mean inter-assay precision, measured as the percentage CV for each of the concentration pools, was 3.8%–5.1% for amoxicillin, 4.1%–6.0% for ciprofloxacin, 3.9%–13.3% for metronidazole, 5.4%–22.1% for hydroxymetronidazole, and 4.7%–6.1% for sulfamethoxazole. The upper estimates of precision for metronidazole and hydroxymetronidazole were inflated by two values each in the high-QC pool, which likely resulted from erroneous inclusion in this pool of two samples from the medium-QC pool. When these outlier results were excluded, the upper estimates of precision were reduced to 6.9% and 9.6% for metronidazole and hydroxymetronidazole, respectively. The mean inter-assay accuracy, expressed as the percentage of difference of the mean value for each pool from the theoretical concentration, ranged from –6.0% to –2.0% for amoxicillin, 0.8% to 4.0% for ciprofloxacin, –5.4% to –1.3% for metronidazole, –4.5% to –2.0% for hydroxymetronidazole, and –2.3% to –1.6% for sulfamethoxazole. In addition, 94% of the sulfamethoxazole, 89% of the metronidazole, and 85% of the hydroxymetronidazole incurred sample reproducibility results were within ±20% of the mean of the original and re-assay results, meeting the predefined acceptance criteria.

Pharmacokinetic parameters were determined from the plasma concentration–time data for amoxicillin, ciprofloxacin, metronidazole, or sulfamethoxazole by non-compartmental analysis using WinNonlin® Professional (Pharsight Corp, Mountain View, CA, USA), version 5.1.1.

Pharmacokinetic parameters for amoxicillin and ciprofloxacin (single daily dosing antibiotics) included:

- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Area under the plasma concentration–time curve (AUC) from time zero to last measurable concentration (C_t) at time t (AUC_{0-t}), and from zero to infinity ($AUC_{0-\infty}$), calculated as $AUC_{0-t} + (C_t/\lambda_z)$
- Apparent terminal phase disposition half-life ($t_{1/2}$)
- Apparent terminal phase disposition rate constant (λ_z)
- Apparent oral-dose clearance (CL/F), calculated as dose/$AUC_{0-\infty}$
- Apparent volume of distribution (Vz/F), calculated as dose/$(AUC \cdot \lambda_z)$

Pharmacokinetic parameters for metronidazole (and metabolite hydroxymetronidazole) and sulfamethoxazole (repeated daily dosing antibiotics) included:

- C_{max} at steady state (C_{maxss})
- Minimum plasma concentration at steady state (C_{minss})
- t_{max}
- AUC within a dosing interval at steady state (0–12 hours, AUC_{ss}) and within a 24-hour period at steady state (AUC_{0-24})
- Degree of fluctuation (DF), calculated as $([C_{maxss} - C_{minss}]/C_{av})$, where $C_{av} = AUC_{ss}/12$.

In prior literature pertaining to the sample size in study 1, intra-subject CVs have been reported for the log-transformed parameters of amoxicillin $AUC_{0-\infty}$ and C_{max} of 15.4% and

16.8%, respectively,[41] and 27.4% and 27.6%, respectively.[47] In other literature, intra-subject variability for amoxicillin has been reported between 20% and 30%.[42] To demonstrate equivalence between amoxicillin administered with MMX mesalamine and amoxicillin administered with placebo, allowing for a 5% difference in true means (ratio of 1.05), and a within-subject CV of 30%, 52 subjects were required to achieve 90% power.

In prior literature pertaining to the sample size in study 2, intra-subject CVs have been reported for the log-transformed parameters of ciprofloxacin XR AUC_{0-t} and C_{max} of 12.22% and 18.04%, respectively,[43] and 12.45% and 16.34%, respectively.[44] To demonstrate equivalence between ciprofloxacin XR administered with MMX mesalamine and ciprofloxacin XR administered with placebo, allowing for a 5% difference in true means (ratio of 1.05) and a within-subject CV of 20%, 24 subjects were required to achieve 90% power. The number of subjects to be randomized was increased to 62 and 30 for studies 1 and 2, respectively, to allow for dropouts.

In prior literature pertaining to the sample size in study 3, intra-subject CVs have been reported for the log-transformed parameters of metronidazole AUC_{0-t} and C_{max} of 9.5% and 6.9%, respectively.[45] To demonstrate equivalence between metronidazole administered with MMX mesalamine and metronidazole administered with placebo, allowing for a 5% difference in true means (ratio of 1.05) and a within-subject CV of 10%,[45] eight subjects were required to achieve 90% power. However, FDA guidance on bioavailability and bioequivalence studies consider that an appropriate bioequivalence design should include a minimum of 12 subjects.[49] Also, given the paucity of data available regarding the variability of metronidazole pharmacokinetics, it was recommended conservatively that 24 subjects (corresponding to a within-subject CV of 20%) should be recruited to the study.

In study 4, no prior data on the intra-subject variability of pharmacokinetic parameters for sulfamethoxazole were available. Inter-subject CVs were reported for the log-transformed parameters of C_{max} of 14.56% and 16.89%, and AUC_{0-t} of 25.28% and 24.45%, for reference and trial arms of sulfamethoxazole, respectively. Bioequivalence was achieved, and there were no significant differences in inter-subject variation between treatments.[46] To demonstrate equivalence between sulfamethoxazole administered with MMX mesalamine and sulfamethoxazole administered with placebo, allowing for a 5% difference in true means (ratio of 1.05) and a within-subject CV of 24%,[51] 36 subjects were required to achieve 90% power. Up to 44 subjects were enrolled to allow for dropouts.

Means of log-transformed bioavailability parameters (C_{max} and AUC for amoxicillin and ciprofloxacin XR; C_{maxss} and AUC_{ss} for metronidazole, hydroxymetronidazole, and sulfamethoxazole) were compared between treatments using an analysis of variance model with period and treatment regimen as fixed effects and subject nested-within-sequence as a random effect, using SAS PROC MIXED (SAS Institute Inc., Cary, NC, USA). The geometric mean ratios and 90% confidence intervals (CIs) of antibiotic in combination with MMX mesalamine to antibiotic administered with placebo were used to estimate the magnitude of treatment regimen differences in C_{max} and AUC (or C_{maxss} and AUC_{ss}), and to test the primary hypothesis in each study of an effect of MMX mesalamine on antibiotic pharmacokinetics. If the 90% CI fell within the interval (0.80–1.25), then the hypothesis that MMX mesalamine has an effect on antibiotic pharmacokinetics was rejected. In contrast, if the 90% CI was not contained in the interval (0.80–1.25), then the hypothesis that MMX mesalamine has an effect on the pharmacokinetics of the antibiotic could not be excluded, and clinical significance was assessed. t_{max} values were compared nonparametrically between treatment arms in each study using the Wilcoxon signed rank test.

Safety

Safety evaluations in the four studies included the assessment of adverse events (AEs), clinical laboratory parameters, vital signs, electrocardiograms, and physical examination findings at regular intervals. Subjects were questioned in a general way to ascertain whether AEs had occurred, and both spontaneous reports of AEs, as well as AEs that were observed by the investigator or observed by a staff member and confirmed by the investigator, were recorded. The investigator categorized the intensity (severity) of the AE and its relationship to the investigational product. Blood samples for standard clinical laboratory tests (serum biochemistry, hematology, and urinalysis) were obtained at protocol-specified time points throughout the study, and the tests were performed by Physicians Reference Laboratory (Overland Park, KS, USA). Vital signs included systolic and diastolic blood pressures and heart rate.

Results

Study 1: amoxicillin and MMX mesalamine

Subject disposition and baseline characteristics

Study 1 was conducted from October 7, 2011 (first date of informed consent/screening) through November 20, 2011 (last subject study visit/follow-up assessment). Of the

62 randomized subjects (74% male), 59 completed the study and three subjects discontinued (all during the placebo + amoxicillin arm), including one due to an AE. The safety analysis set included all subjects who took at least one dose of investigational product and had at least one post-dose safety assessment (n=62); the pharmacokinetic analysis set included all in the safety set with sufficient and interpretable pharmacokinetic data (n=61). Subject demographics and baseline characteristics for all four studies are summarized in Table 1. In each study, subjects in each treatment sequence AB (placebo + antibiotic/MMX mesalamine + antibiotic) and BA (MMX mesalamine + antibiotic/placebo + antibiotic) were matched for all demographic and baseline characteristics.

Pharmacokinetics

Mean amoxicillin plasma concentrations over time for each treatment regimen are presented in Figure 1. Plasma pharmacokinetic parameters for amoxicillin were generally similar across the two treatment regimens (Table 2). In both

Table 1 Subject demographics

Characteristic	Study 1: Amoxicillin			Study 2: Ciprofloxacin XR		
	Placebo + amoxicillin/ MMX mesalamine + amoxicillin (n=31)	MMX mesalamine + amoxicillin/ placebo + amoxicillin (n=31)	Total (N=62)	Placebo + ciprofloxacin/ MMX mesalamine + ciprofloxacin (n=15)	MMX mesalamine + ciprofloxacin/ placebo + ciprofloxacin (n=15)	Total (N=30)
Mean age (SD), y	34.3 (11.2)	30.1 (8.9)	32.2 (10.3)	31.9 (11.7)	31.3 (11.0)	31.6 (11.2)
Sex, n (%)						
Male	24 (77.4)	22 (71.0)	46 (74.2)	10 (66.7)	10 (66.7)	20 (66.7)
Female	7 (22.6)	9 (29.0)	16 (25.8)	5 (33.3)	5 (33.3)	10 (33.3)
Mean weight (SD), kg	77.5 (13.7)	75.8 (12.9)	76.7 (13.2)	79.0 (14.8)	77.0 (13.5)	78.0 (13.9)
Mean BMI (SD), kg/m^2	25.5 (3.3)	25.2 (3.1)	25.3 (3.2)	26.5 (3.3)	25.3 (3.1)	25.9 (3.2)
Race, n (%)						
White	21 (67.7)	18 (58.1)	39 (62.0)	8 (53.3)	9 (60.0)	17 (56.7)
Black/African American	9 (29.0)	10 (32.3)	23 (37.1)	6 (40.0)	6 (40.0)	12 (40.0)
Asian	0	0	0	1 (6.7)	0	1 (3.3)
Other	1 (3.2)	3 (9.7)	4 (6.5)	0	0	0
Ethnicity, n (%)						
Hispanic or Latino	4 (12.9)	4 (12.9)	8 (12.9)	2 (13.3)	1 (6.7)	3 (10.0)
Not Hispanic or Latino	27 (87.1)	27 (87.1)	54 (87.1)	13 (86.7)	14 (93.3)	27 (90.0)
	Study 3: Metronidazole			**Study 4: Sulfamethoxazole**		
	Placebo + metronidazole/ MMX mesalamine + metronidazole (n=15)	MMX mesalamine + metronidazole/ placebo + metronidazole (n=15)	Total (N=30)	Placebo + sulfamethoxazole/ MMX mesalamine + sulfamethoxazole (n=22)	MMX mesalamine + sulfamethoxazole/ placebo + sulfamethoxazole (n=22)	Total (N=44)
Mean age (SD), y	35.9 (8.8)	31.2 (11.0)	33.6 (10.1)	38.0 (11.7)	35.4 (12.6)	36.7 (12.0)
Sex, n (%)						
Male	9 (60)	9 (60)	18 (60)	12 (54.5)	12 (54.5)	24 (54.5)
Female	6 (40)	6 (40)	12 (40)	10 (45.5)	10 (45.5)	20 (45.5)
Mean weight (SD), kg	77.9 (6.97)	78.9 (16.6)	78.4 (12.5)	78.0 (11.6)	72.3 (11.4)	75.2 (11.7)
Mean BMI (SD), kg/m^2	26.6 (2.3)	25.0 (3.0)	25.8 (2.7)	26.5 (2.4)	25.4 (3.2)	26.0 (2.9)
Race, n (%)						
White	7 (46.7)	8 (53.3)	15 (50.0)	14 (63.6)	12 (54.5)	26 (59.1)
Black/African American	8 (53.3)	7 (46.7)	15 (50.0)	6 (27.3)	10 (45.5)	16 (36.4)
Asian	0	0	0	1 (4.5)	0	1 (2.3)
Other	0	0	0	1 (4.5)	0	1 (2.3)
Ethnicity, n (%)						
Hispanic or Latino	1 (6.7)	0	1 (3.3)	0 (0)	1 (4.5)	1 (2.3)
Not Hispanic or Latino	14 (93.3)	15 (100)	29 (96.7)	22 (100)	21 (95.5)	43 (97.7)

Note: MMX® is a registered trademark of Cosmo Technologies Ltd, Wicklow, Ireland.
Abbreviations: BMI, body mass index; SD, standard deviation; XR, extended release; y, years.

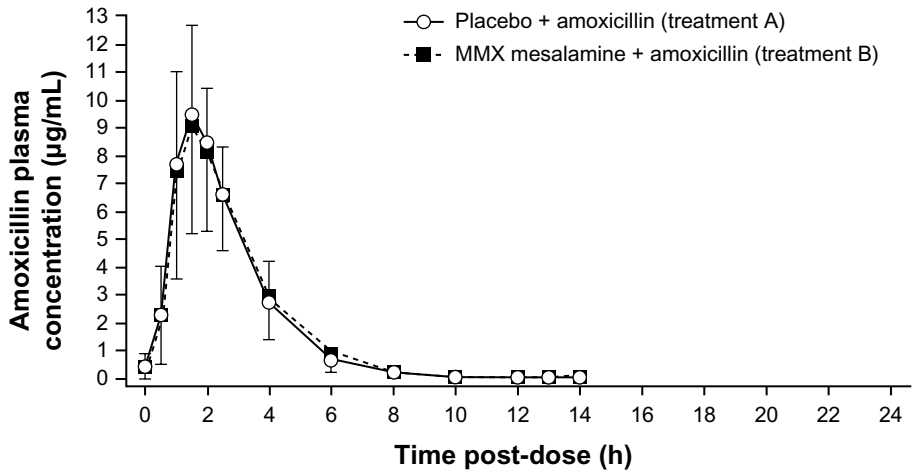

Figure 1 Study 1: Mean (SD) amoxicillin plasma concentrations versus time for amoxicillin coadministered with placebo or with MMX® mesalamine (Cosmo Technologies Ltd, Wicklow, Ireland). Treatment A consisted of placebo administered orally once daily on days 1–4 plus a single oral dose of amoxicillin 500 mg on day 4. Treatment B consisted of MMX mesalamine 4.8 g administered orally once daily on days 1–4 plus a single oral dose of amoxicillin 500 mg on day 4.
Note: The error bar rises above the mean data point for treatment A and falls below the mean data point for treatment B.
Abbreviations: SD, standard deviation; h, hours.

treatment regimens, amoxicillin was rapidly absorbed, with a median t_{max} of 1.5 hours in both treatment arms, and rapidly eliminated, with a mean $t_{1/2}$ of 1.4–1.5 hours, regardless of treatment regimen. CL/F and Vz/F also appeared similar in both treatment groups.

Treatment with MMX mesalamine had no statistically significant effects on systemic exposure to amoxicillin following coadministration with amoxicillin (Table 2). The 90% CIs around the geometric mean ratios for C_{max}, $AUC_{0-\infty}$, and AUC_{0-t} fell entirely within the predefined equivalence range of 0.80–1.25. Amoxicillin t_{max} values were unaffected by coadministration with MMX mesalamine, with a median difference between treatments of 0.0 hours, and a 90% CI ranging from –0.05 to 1.50 hours.

Safety

Treatment-emergent AEs (TEAEs) were experienced by 22% (13/59) of subjects receiving MMX mesalamine plus amoxicillin and 15% (9/62) of subjects on placebo plus amoxicillin. The most common TEAE in either treatment arm was headache,

Table 2 Pharmacokinetic parameters of amoxicillin

Plasma pharmacokinetic parameters of amoxicillin			
Parameter, mean (SD)[a]	**Placebo + amoxicillin (n=60)[a]**	**MMX mesalamine + amoxicillin (n=59)[a]**	
AUC_{0-t}, h·µg/mL	27.5 (5.02)	27.9 (6.32)	
$AUC_{0-\infty}$, h·µg/mL	27.8 (5.02)	28.3 (6.37)	
CL/F, L/h	18.6 (3.50)	18.5 (4.01)	
C_{max}, µg/mL	10.3 (2.59)	10.2 (2.89)	
t_{max} median (range), h	1.50 (1.00–4.00)	1.50 (1.00–4.00)	
Vz/F, L	36.9 (12.0)	39.3 (17.8)	
$t_{1/2}$, h	1.39 (0.379)	1.50 (0.671)	
Effect of MMX mesalamine on the systemic exposure to amoxicillin			
Parameter	**Placebo + amoxicillin[b]**	**MMX mesalamine + amoxicillin[b]**	**Geometric LS mean ratio (90% CI), (MMX mesalamine + amoxicillin)/ (placebo + amoxicillin)**
C_{max}, µg/mL	9.90	9.81	0.991 (0.940, 1.04)
AUC_{0-t}, h·µg/mL	26.8	27.3	1.02 (0.993, 1.04)
$AUC_{0-\infty}$, h·µg/mL	27.1	27.6	1.02 (0.995, 1.04)

Notes: MMX® is a registered trademark of Cosmo Technologies Ltd, Wicklow, Ireland. [a]Mean (SD) presented for all parameters except t_{max}, which is presented as median (range); [b]geometric least squares mean.
Abbreviations: AUC, area under the plasma concentration–time curve; AUC_{0-t}, AUC from time zero to the last measurable concentration at time t; $AUC_{0-\infty}$, AUC from time zero to infinity; CI, confidence interval; CL/F, apparent oral-dose clearance; C_{max}, maximum plasma concentration; $t_{1/2}$, apparent terminal phase disposition half-life; t_{max}, time to C_{max}; Vz/F, apparent volume of distribution; LS, least squares; SD, standard deviation; h, hours.

reported in four (7%) subjects in the placebo arm and in three (5%) subjects in the MMX mesalamine plus amoxicillin arm. All TEAEs were of mild intensity, except for four TEAEs (two in each treatment arm) that were considered to be of moderate intensity (headache [two occurrences], constipation, and vomiting). Four drug-related TEAEs (headache and somnolence in MMX mesalamine plus amoxicillin; diarrhea and vomiting in placebo plus amoxicillin) were reported. No deaths, serious AEs, or discontinuations by the investigator due to AEs occurred, and all AEs resolved by study completion. One subject reported an upper respiratory tract infection during the washout period between treatments; this subject discontinued from the study before dosing on the second treatment began.

Study 2: ciprofloxacin and MMX mesalamine

Subject disposition and baseline characteristics

Study 2 was conducted from July 25, 2011 through August 24, 2011. A total of 30 subjects (67% male) were randomized; 29 subjects completed the study, and one subject who experienced a TEAE (phlebitis during the MMX mesalamine + ciprofloxacin XR arm) discontinued. The safety and pharmacokinetic analysis sets in study 2 included all 30 randomized subjects.

Pharmacokinetics

Mean ciprofloxacin plasma concentrations over time for each treatment regimen are presented in Figure 2. Plasma pharmacokinetic parameters of ciprofloxacin were generally similar across the two treatment regimens (Table 3). Ciprofloxacin was rapidly absorbed, with a median t_{max} of 2 hours for both treatments, and was also rapidly eliminated, with a $t_{1/2}$ of approximately 4.8 hours for both treatments. CL/F and Vz/F also appeared similar in both treatment groups.

Treatment with MMX mesalamine had no statistically significant effects on the systemic exposure of ciprofloxacin, following coadministration with ciprofloxacin XR (Table 3). The 90% CIs around the geometric mean ratios for C_{max}, $AUC_{0-\infty}$, and AUC_{0-t} fell entirely within the predefined equivalence range of 0.80–1.25. Ciprofloxacin t_{max} values were also unaffected by coadministration with MMX mesalamine, as indicated by a median difference between treatments of 0.0 hours, with a 90% CI range of –1.00 to 1.00 hours.

Safety

Three TEAEs were experienced by 7% (2/29) of subjects on placebo plus ciprofloxacin XR, and 27% (8/30) of subjects on MMX mesalamine plus ciprofloxacin XR experienced eleven TEAEs. The most common TEAE in subjects receiving MMX mesalamine plus ciprofloxacin XR was headache, reported by two subjects. Twelve of the 14 reported TEAEs were mild, and two moderate AEs (cellulitis and phlebitis) occurred in one subject in the MMX mesalamine plus ciprofloxacin XR arm. Of the 14 TEAEs, four (flatulence, gastroesophageal reflux disease, nausea, and fatigue) were considered related to MMX mesalamine plus ciprofloxacin XR, and one TEAE (nausea) was considered related to ciprofloxacin XR plus placebo. No deaths or serious AEs were reported, although one subject was withdrawn from the study due to moderate phlebitis considered not related to the investigational products. All AEs reported in study 2 were resolved by study completion.

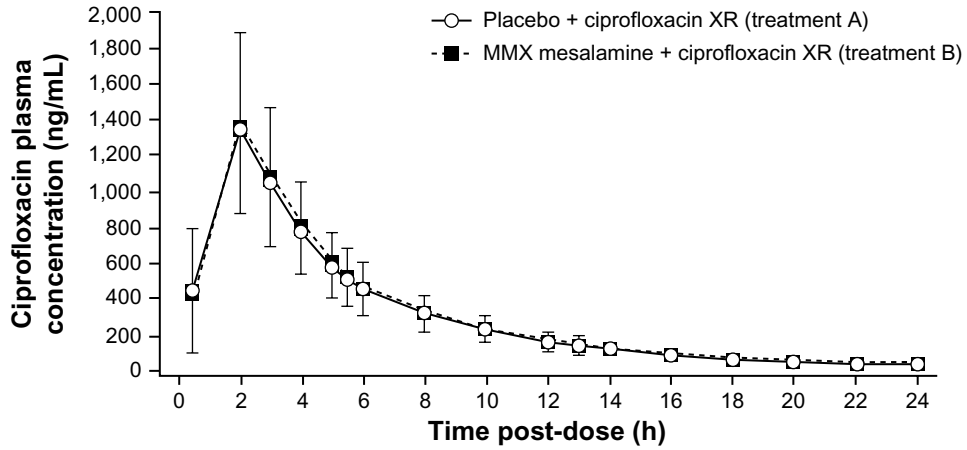

Figure 2 Study 2: Mean (SD) ciprofloxacin XR plasma concentrations versus time for ciprofloxacin XR coadministered with placebo or with MMX® mesalamine (Cosmo Technologies Ltd, Wicklow, Ireland). Treatment A consisted of placebo administered once daily on days 1–4 plus a single oral dose of ciprofloxacin XR 500 mg on day 4. Treatment B consisted of MMX mesalamine 4.8 g given once daily on days 1–4 plus a single oral dose of ciprofloxacin XR 500 mg on day 4.
Note: The error bar rises above the mean data point for treatment A and falls below the mean data point for treatment B.
Abbreviations: SD, standard deviation; XR, extended release; h, hours.

Table 3 Pharmacokinetic parameters of ciprofloxacin

Plasma pharmacokinetic parameters of ciprofloxacin		
Parameter, mean (SD)[a]	**Placebo + ciprofloxacin XR (n=29)[a]**	**MMX mesalamine + ciprofloxacin XR (n=30)[a]**
AUC_{0-t}, h · ng/mL	7,530 (1,919)	7,650 (2,060)
$AUC_{0-\infty}$, h · ng/mL	7,805 (1,949)	7,934 (2,101)
CL/F, L/h	69.4 (22.8)	67.8 (19.3)
C_{max}, ng/mL	1,455 (518)	1,433 (446)
λ_z, 1/h	0.1482 (0.01934)	0.1477 (0.020007)
t_{max} median (range), h	2.00 (0.50–4.00)	2.00 (0.50–3.00)
Vz/F, L	482 (184)	476 (182)
$t_{1/2}$, h	4.75 (0.59)	4.79 (0.73)

Effect of MMX mesalamine on the systemic exposure to ciprofloxacin			
Parameter	**Placebo + ciprofloxacin XR[b]**	**MMX mesalamine + ciprofloxacin XR[b]**	**Geometric LS mean ratio (90% CI), (MMX mesalamine + ciprofloxacin XR)/ (placebo + ciprofloxacin XR)**
C_{max}, ng/mL	1,369	1,367	0.999 (0.893, 1.117)
AUC_{0-t}, h · ng/mL	7,286	7,371	1.012 (0.929, 1.101)
$AUC_{0-\infty}$, h · ng/mL	7,558	7,655	1.013 (0.933, 1.100)

Notes: MMX® is a registered trademark of Cosmo Technologies Ltd, Wicklow, Ireland. [a]Mean (SD) presented for all parameters except t_{max}, which is presented as median (range); [b]geometric least squares mean.

Abbreviations: AUC, area under the plasma concentration–time curve; AUC_{0-t}, AUC from time zero to the last measurable concentration at time t; $AUC_{0-\infty}$, AUC from time zero to infinity; CL/F, apparent oral-dose clearance; C_{max}, maximum plasma concentration; $t_{1/2}$, apparent terminal phase disposition half-life; t_{max}, time to C_{max}; Vz/F, apparent volume of distribution; LS, least squares; CI, confidence interval; λ_z, apparent terminal phase disposition rate constant; SD, standard deviation; h, hours.

Study 3: metronidazole and MMX mesalamine

Subject disposition and baseline characteristics

Study 3 was conducted from August 22, 2011 through October 5, 2011. Of the 30 subjects (60% male) randomized to study 3, 27 completed the study, and three discontinued (none due to AEs). The safety analysis set included all 30 subjects; the pharmacokinetic analysis set included 29 subjects.

Pharmacokinetics

Mean metronidazole and hydroxymetronidazole plasma concentrations over time for each treatment regimen are presented in Figure 3A and B. Plasma pharmacokinetic parameters for metronidazole and hydroxymetronidazole were generally similar between the two treatment regimens (Table 4). In both treatment regimens, metronidazole was rapidly absorbed, with a median t_{max} of approximately 1 hour; hydroxymetronidazole had a median t_{max} of 4 hours for both treatment arms. DF was similar in both treatment arms for metronidazole (~1.0) and hydroxymetronidazole (~0.2). Treatment with MMX mesalamine had no statistically significant effects on the systemic exposure to metronidazole or hydroxymetronidazole (Table 4). For both metronidazole and hydroxymetronidazole, the 90% CIs around the geometric mean ratios (metronidazole + MMX mesalamine: metronidazole + placebo) for C_{maxss} and AUC_{ss} fell entirely within the predefined equivalence range of 0.80–1.25. Metronidazole and hydroxymetronidazole t_{max} values were also unaffected by coadministration with MMX mesalamine, with median differences (metronidazole + MMX mesalamine: metronidazole + placebo) of 0.000 hours (90% CI, −1.000 to 1.433 hours) and 0.000 hours (90% CI, −2.000 to 6.000 hours), respectively.

Safety

In this study, 14 TEAEs were reported by 20.7% (6/29) of subjects on MMX mesalamine plus metronidazole, and 13 TEAEs were reported by 17.2% (5/29) of subjects on placebo plus metronidazole. The most common TEAE was headache (three subjects in the MMX mesalamine arm and four subjects in the placebo arm). Most (25/27) TEAEs were considered mild; two moderate AEs (nausea and vomiting) occurred in the same subject in the MMX mesalamine plus metronidazole group. Thirteen of the 27 TEAEs (including abdominal pain, diarrhea, nausea, headache, vomiting, and diaphoresis) were considered related to MMX mesalamine or metronidazole, and ten TEAEs (including nausea, headache, vomiting, abdominal pain, and diarrhea) were considered related to metronidazole coadministered with placebo. No deaths, serious AEs, or AEs leading to study withdrawal were reported. All AEs resolved by completion of the study, except for neck pain in one subject, which was not considered related to the investigational products.

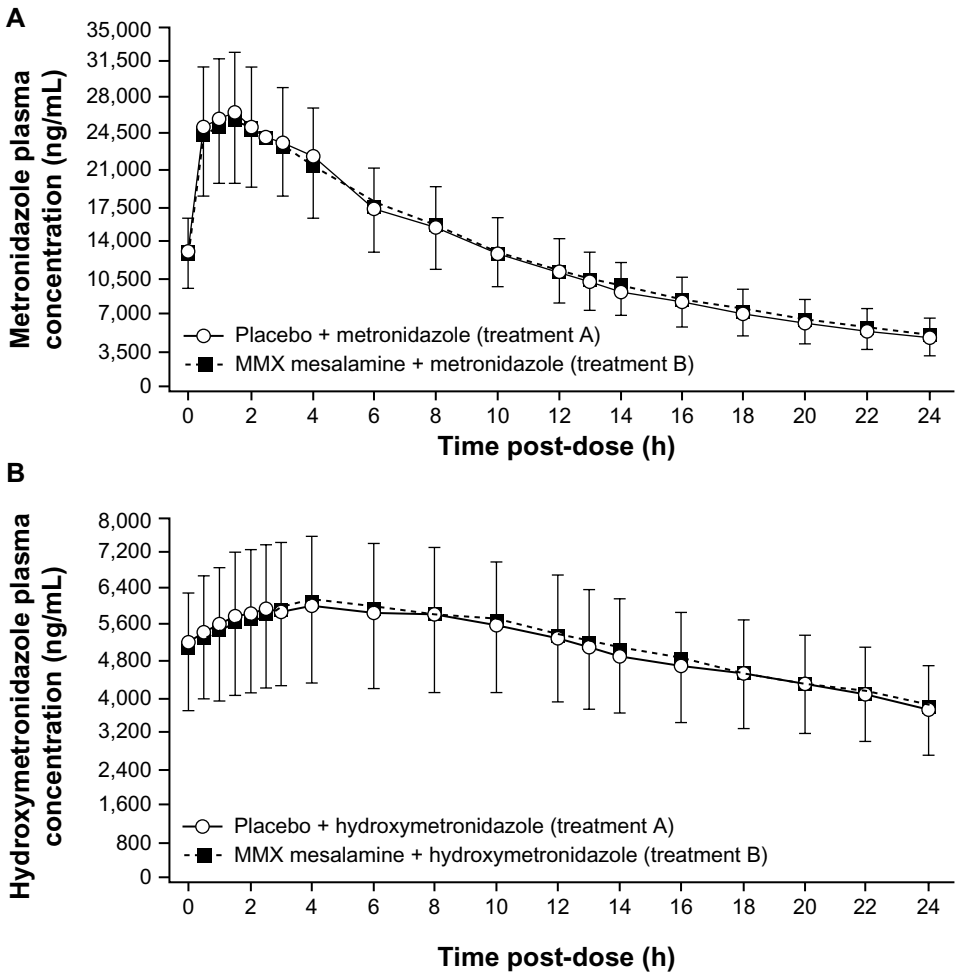

Figure 3 Study 3: Mean (SD) metronidazole (**A**) and hydroxymetronidazole (**B**) plasma concentrations versus time for metronidazole coadministered with placebo or with MMX® mesalamine (Cosmo Technologies Ltd, Wicklow, Ireland). Treatment A consisted of placebo administered orally once daily on days 1–4 plus metronidazole 750 mg twice daily on days 1–3 and a single dose of metronidazole 750 mg on day 4. Treatment B consisted of MMX mesalamine 4.8 g once daily on days 1–4 plus metronidazole 750 mg twice daily on days 1–3 and a single dose of metronidazole 750 mg on day 4.
Note: The error bar rises above the mean data point for treatment A and falls below the mean data point for treatment B.
Abbreviations: SD, standard deviation; h, hours.

Study 4: sulfamethoxazole and MMX mesalamine

Subject disposition and baseline characteristics

Study 4 was conducted from November 7, 2011 through December 20, 2011. A total of 44 subjects (54.5% male) were randomized; of these, 42 completed the study, and two discontinued (none due to AEs). The safety and pharmacokinetic analysis sets in study 4 included all 44 randomized subjects.

Pharmacokinetics

Mean sulfamethoxazole plasma concentrations over time for each treatment regimen are presented in Figure 4. Mean sulfamethoxazole plasma concentrations in subjects receiving MMX mesalamine plus sulfamethoxazole were slightly higher than in subjects receiving placebo plus sulfamethoxazole. Plasma pharmacokinetic parameters of sulfamethoxazole were of a similar order of magnitude for the two treatment regimens (Table 5). Sulfamethoxazole was rapidly absorbed in both treatment regimens, with a median t_{max} of 2 hours. DF decreased by 12%, from 0.689 to 0.604, when sulfamethoxazole was coadministered with MMX mesalamine compared with coadministration with placebo.

Sulfamethoxazole exposure increased to a statistically significant extent when coadministered with MMX mesalamine compared with when coadministered with placebo (Table 5), as the 90% CIs around the geometric mean ratios (sulfamethoxazole + MMX mesalamine: sulfamethoxazole + placebo) for both C_{maxss} and AUC_{ss} of sulfamethoxazole did not include the value 1.00. Treatment with MMX mesalamine increased the point estimates of the geometric mean ratios of sulfamethoxazole C_{maxss} and AUC_{ss} by 12% and 15%,

Table 4 Pharmacokinetic parameters of metronidazole and hydroxymetronidazole

Plasma pharmacokinetic parameters of metronidazole and hydroxymetronidazole

Parameter	Metronidazole[a]		Hydroxymetronidazole[a]	
	Placebo + metronidazole (n=29)	MMX mesalamine + metronidazole (n=29)	Placebo + metronidazole (n=29)	MMX mesalamine + metronidazole (n=29)
AUC_{ss}, h · ng/mL	217,686 (49,693)	215,809 (48,681)	69,009 (16,734)	69,069 (19,409)
AUC_{0-24}, h · ng/mL	306,004 (76,627)	304,386 (74,308)	123,189 (29,429)	123,664 (33,371)
C_{maxss}, ng/mL	28,193 (6,249)	28,057 (5,522)	6,376 (1,551)	6,297 (1,777)
C_{minss}, ng/mL	10,936 (3,144)	10,932 (2,986)	4,981 (1,203)	4,881 (1,333)
t_{max}, h	1.00 (0.50–3.00)	1.01 (0.50–3.00)	4.00 (0.0–8.0)	4.00 (1.5–10.0)
DF	0.971 (0.222)	0.983 (0.282)	0.242 (0.0687)	0.245 (0.0638)

Effect of MMX mesalamine on the systemic exposure to metronidazole and hydroxymetronidazole

Parameter	Placebo + metronidazole[b]	MMX mesalamine + metronidazole[b]	Geometric LS mean ratio (90% CI), (MMX mesalamine + metronidazole)/ (placebo + metronidazole)
Metronidazole			
C_{maxss}, ng/mL	27,559	27,364	0.993 (0.951, 1.04)
AUC_{ss}, h · ng/mL	212,473	208,112	0.979 (0.961, 0.998)
Hydroxymetronidazole			
C_{maxss}, ng/mL	6,180	6,034	0.976 (0.936, 1.02)
AUC_{ss}, h · ng/mL	66,883	66,123	0.989 (0.947, 1.03)

Notes: MMX® is a registered trademark of Cosmo Technologies Ltd, Wicklow, Ireland. [a]All parameters presented as mean (SD), except t_{max}, which is presented as median (range); [b]geometric least squares mean.

Abbreviations: AUC, area under the plasma concentration–time curve; AUC_{ss}, AUC within a dosing interval at steady state (0–12 hours); AUC_{0-24}, AUC within a 24-hour period at steady state; CI, confidence interval; C_{maxss}, maximum plasma concentration at steady state; C_{minss}, minimum plasma concentration at steady state; t_{max}, time to C_{maxss}; DF, degree of fluctuation; LS, least squares; SD, standard deviation; h, hours.

respectively. However, the differences in exposure were not considered to be clinically significant, because for both parameters, the 90% CIs fell entirely within the predefined equivalence range of 0.80–1.25. Sulfamethoxazole t_{max} values were also unaffected by coadministration with MMX mesalamine, with a median difference (sulfamethoxazole + MMX mesalamine: sulfamethoxazole + placebo) of 0.25 hours (90% CI, –2.00 to 2.50 hours). Therefore, MMX mesalamine did not have a clinically significant effect on the pharmacokinetics of sulfamethoxazole.

Safety

Twenty TEAEs were reported by 31.8% (14/44) of subjects receiving MMX mesalamine plus sulfamethoxazole, and

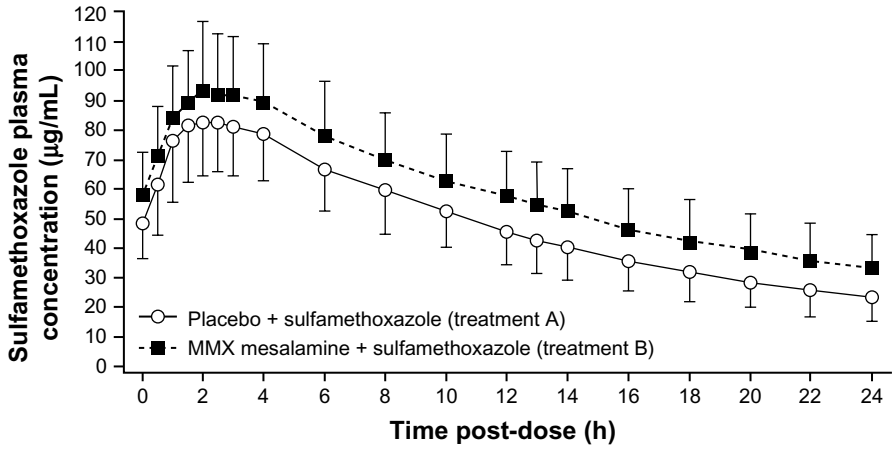

Figure 4 Study 4: Mean (SD) sulfamethoxazole plasma concentrations versus time for sulfamethoxazole coadministered with placebo or with MMX® mesalamine (Cosmo Technologies Ltd, Wicklow, Ireland). Treatment A consisted of placebo administered orally once daily on days 1–4 plus sulfamethoxazole 800 mg/trimethoprim 160 mg twice daily on days 1–3 and a single dose of sulfamethoxazole 800 mg/trimethoprim 160 mg on day 4. Treatment B consisted of MMX mesalamine 4.8 g once daily on days 1–4 plus sulfamethoxazole 800 mg/trimethoprim 160 mg twice daily on days 1–3 and a single dose of sulfamethoxazole 800 mg/trimethoprim 160 mg on day 4.

Note: The error bar rises above the mean data point for treatment A and falls below the mean data point for treatment B.

Abbreviations: SD, standard deviation; h, hours.

Table 5 Pharmacokinetic parameters of sulfamethoxazole

Plasma pharmacokinetic parameters of sulfamethoxazole

Parameter	Placebo + sulfamethoxazole (n=43)[a]	MMX mesalamine + sulfamethoxazole (n=43)[a]
AUC_{ss}, h·μg/mL	786 (169)	909 (198)
AUC_{0-24}, h·μg/mL	1,176 (275)	1,430 (352)
C_{maxss}, μg/mL	89.1 (16.3)	100 (20.2)
C_{minss}, μg/mL	45.1 (11.4)	55.4 (14.6)
t_{max}, h	2.00 (1.00–4.00)	2.00 (0.50–4.00)
DF	0.689 (0.140)	0.604 (0.138)

Effect of MMX mesalamine on the systemic exposure to sulfamethoxazole

Parameter	Placebo + sulfamethoxazole[b]	MMX mesalamine + sulfamethoxazole[b]	Geometric LS mean ratio (90% CI), (MMX mesalamine + sulfamethoxazole)/ (placebo + sulfamethoxazole)
C_{maxss}, μg/mL	87.5	97.8	1.12 (1.09, 1.15)
AUC_{ss}, h·μg/mL	768	882	1.15 (1.12, 1.18)

Notes: MMX® is a registered trademark of Cosmo Technologies Ltd, Wicklow, Ireland. [a]All parameters presented as mean (SD), except t_{max}, which is presented as median (range); [b]geometric least squares mean.

Abbreviations: AUC, area under the plasma concentration–time curve; AUC_{ss}, AUC within a dosing interval at steady state (0–12 hours); AUC_{0-24}, AUC within a 24-hour period at steady state; CI, confidence interval; C_{maxss}, maximum plasma concentration at steady state; C_{minss}, minimum plasma concentration at steady state; t_{max}, time to C_{maxss}; DF, degree of fluctuation; LS, least squares; SD, standard deviation; h, hours.

13 TEAEs were reported by 23.3% (10/43) of subjects on placebo plus sulfamethoxazole. Gastrointestinal disorders were the most common TEAEs reported in both treatment groups (seven subjects in the MMX mesalamine arm and four subjects in the placebo arm). Most (25/33) TEAEs were considered mild; four TEAEs in the MMX mesalamine group (headache, n=3; and vomiting, n=1) and four TEAEs in the placebo group (headache, n=2; back pain and constipation, n=1 each) were considered moderate. Eleven TEAEs (headache, nausea, abdominal distension, constipation, diarrhea, vomiting, dry mouth, and nervousness) were considered related to MMX mesalamine plus sulfamethoxazole, and two TEAEs (flatulence and headache) were considered related to sulfamethoxazole coadministered with placebo. No deaths, serious AEs, or AEs leading to study withdrawal were reported. All AEs resolved by completion of the study.

Discussion and conclusion

Management of UC involves use of long-term maintenance therapy with 5-ASAs, such as MMX mesalamine. Given that patients with UC require long-term therapy, they are likely to require concomitant treatment with other medications, such as antibiotics.[9] The current studies assessed the effect of MMX mesalamine on the pharmacokinetics of four commonly prescribed antibiotics in healthy adult subjects. Results from the four studies presented here indicate that treatment with MMX mesalamine had no clinically significant effect on the pharmacokinetics of single oral doses of amoxicillin or ciprofloxacin XR, or of repeated doses of metronidazole or sulfamethoxazole. The safety profiles of all four antibiotics coadministered with MMX mesalamine were no different from those seen for each of the antibiotics administered alone.

Across studies 1, 2, and 3, respectively, MMX mesalamine had no significant effect on the pharmacokinetics of amoxicillin, ciprofloxacin, and metronidazole in healthy subjects. After a 500 mg single dose of amoxicillin or ciprofloxacin or a 750 mg twice-daily dose of metronidazole, plasma concentration–time curves, and steady-state pharmacokinetic parameters of each of the antibiotics were similar in the presence or absence of MMX mesalamine. In study 4, sulfamethoxazole exposure was increased to a degree that was statistically significant when sulfamethoxazole 800 mg twice daily was coadministered with MMX mesalamine compared with coadministration with placebo. However, the 90% CIs for the ratios of the primary pharmacokinetic parameters (ie, C_{maxss} and AUC_{ss}) fell entirely within the equivalence acceptance range of 0.80–1.25, and sulfamethoxazole t_{max} values were unaffected by coadministration with MMX mesalamine, indicating that these small differences were not clinically significant. Pharmacokinetic parameters for amoxicillin,[47,52,53] ciprofloxacin,[23] metronidazole,[24] and sulfamethoxazole[25,26,51] were generally consistent with previously published data. Overall, these results suggest that MMX mesalamine does not significantly influence the pharmacokinetics of any of the four studied antibiotics.

In the current studies, amoxicillin, ciprofloxacin, metronidazole, and sulfamethoxazole were all rapidly absorbed, with

median t_{max} values of approximately 1–2 hours. Therefore, the site of absorption of these antibiotics is likely well separated from the terminal ileum/colonic site of absorption of mesalamine when administered as delayed-release MMX mesalamine, which achieves maximum plasma concentrations approximately 8 hours after dose administration.[27]

Following oral administration in the MMX formulation, mesalamine undergoes limited absorption of 21%–22% at steady state,[27] and the absorbed drug is eliminated primarily by metabolism to N-acetyl-mesalamine[28] by NAT-1[34,35] in the liver or colonic mucosa; also, mesalamine does not appear to inhibit cytochrome P450 activity.[33] Unchanged mesalamine and N-acetyl-mesalamine are excreted from the systemic circulation in urine.[33]

The metabolic pathways of amoxicillin, ciprofloxacin, and metronidazole differ from that of MMX mesalamine. Amoxicillin is metabolized to a limited extent to penicilloic acid, which is excreted in the urine, along with unchanged drug (~60% of the dose).[54,55] Ciprofloxacin is eliminated principally by urinary excretion, with nonrenal clearance accounting for approximately one-third of elimination. Approximately 40%–50% of an oral dose of ciprofloxacin is excreted unchanged in the urine. Metabolites (comprising oxo-ciprofloxacin, sulfo-ciprofloxacin, desethylene-ciprofloxacin, and formyl-ciprofloxacin) account for approximately 15% of the dose.[56–58] The metabolic pathway of metronidazole involves primary elimination by cytochrome P450 through hydroxylation to hydroxymetronidazole, an acid metabolite and an oxidation product of the hydroxymetabolite.[59] Regardless of the disparate metabolic pathways, it remained to be confirmed that no interaction existed at the level of renal excretion. Nevertheless, despite the elimination of these three antibiotics and MMX mesalamine converging on the urinary excretion pathway, there was no evidence from data on systemic exposure that the capacity for active renal secretion of amoxicillin, ciprofloxacin, or metronidazole was reduced in the presence of mesalamine.

The limited increase in systemic exposure to sulfamethoxazole in the presence of mesalamine observed in study 4 is consistent with mesalamine and sulfamethoxazole sharing an elimination pathway. After oral administration, sulfamethoxazole is conjugated in the liver by NAT-1 and NAT-2[30,31] to the inactive N4-acetyl metabolite, which represents approximately 15% of circulating drug-related material in the blood.[32] Approximately 80%–100% of administered sulfamethoxazole is rapidly excreted in urine by glomerular filtration and active tubular secretion,[31,60] with 60% of the drug secreted as the N4-acetyl metabolite, and the remainder as unchanged drug or glucuronide.[32] Thus, there is some overlap in the metabolic pathways involved in the elimination of these two drugs, which both include N-acetylation by NAT-1. However, sulfamethoxazole has other routes of elimination (including NAT-2 acetylation, oxidation, glucuronidation, and a significant amount of unchanged renal drug excretion). Moreover, there is lack of evidence from published literature to confirm that either drug is an inhibitor of NAT-1, which would have exacerbated any interaction. Hence, the extent of the interaction between MMX mesalamine and sulfamethoxazole is modest and not of clinical significance.

There were no safety concerns in any of the four studies identified for amoxicillin, ciprofloxacin XR, metronidazole, or sulfamethoxazole after each antibiotic was coadministered with placebo versus with MMX mesalamine, and the observed safety profiles were consistent with previous reports of MMX mesalamine and each antibiotic.

None of the four studies addressed the effect of antibiotic coadministration on the pharmacokinetics of MMX mesalamine. Very large sample sizes (>100 subjects) would have been required in order to determine equivalence by standard acceptance criteria, given the high intra-subject variability of 5-ASA pharmacokinetics. However, the risk of an effect of antibiotic administration on the pharmacokinetics of MMX mesalamine was considered low. Antibiotic administration is typically of a short duration (weeks), whereas maintenance treatment with MMX mesalamine is long term (months or years).

In conclusion, results from these studies suggest that MMX mesalamine does not affect the pharmacokinetics of amoxicillin, ciprofloxacin XR, metronidazole, or sulfamethoxazole and may be coadministered with of any of these antibiotics without impacting their efficacy or safety.

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was involved in the design, collection, analysis, interpretation, and fact checking of information, the content of this manuscript, the ultimate interpretation, and the decision to submit it for publication in *Drug Design, Development, and Therapy* was made by the authors.

Disclosure

David Pierce, retired, is a former employee of Shire and holds stock and/or stock options in Shire. Mary Corcoran, Patrick Martin, and Karen Barrett are employees of Shire and hold stock and/or stock options in Shire. Susi Inglis and Peter Preston are contractors for Shire. Thomas N Thompson and Sandra K Willsie are employees of PRA International, Lenexa, KS, USA, which was contracted by Shire to conduct this research.

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