Rifamycin vs placebo for the treatment of acute uncomplicated diverticulitis: A randomised, double-blind study

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Abstract

Background: Antibiotic treatment in acute uncomplicated diverticulitis (AUD) is commonplace; however, recent studies have questioned their therapeutic efficacy and placebo-controlled studies are scarce.

Aims: A trial was conducted to study the efficacy and safety of the broad-spectrum antibiotic Rifamycin SV multi-matrix (MMX)® (RIF-MMX) colon-specific formulation vs placebo.

Methods: A phase 2 trial was conducted in 201 patients with AUD randomised 2:2:1 to receive oral RIF-MMX 400 mg twice daily (BID) (RIF-800), 600 mg three times daily (RIF-1800) or placebo, for 10 days. The primary endpoint was Day-10 treatment success (required absence of fever, improved left lower quadrant pain, C-reactive protein (CRP) level improvement and no complications). A key secondary endpoint was complete treatment success, requiring additional normalisation of CRP levels.

Results: Day-10 treatment success occurred more frequently in the RIF-800 (62.2%) vs RIF-1800 (49.4%) and placebo groups (47.5%) but fell slightly short of statistical significance (P = 0.06). RIF-800 and RIF-1800 reached significantly (P < 0.05) higher Day 3 complete treatment success rates (11.0% and 12.7%, respectively) vs placebo (0%). Patients with longer duration of baseline AUD attack tended to show higher complete treatment success rates. Adverse drug reactions, most commonly gastrointestinal disorders, occurred in 7.4%, 9.0% and 12.5% of patients taking RIF-800, RIF-1800 and placebo, respectively.

Conclusions: RIF-MMX was well tolerated by most patients, with no safety concerns over 10-day treatment. Patients with longer duration of baseline AUD symptoms might benefit from a short course of antibiotic treatment with the lower dose of RIF-MMX, 400 mg BID. ClinicalTrials.gov number NCT01847664 (EudraCT 2012-003300-13).
Diverticular disease of the colon (DDC) is common in Western countries and is associated with age. Although asymptomatic diverticulosis is a frequent incidental finding in patients undergoing imaging for other indications, symptomatic DDC occurs in 25% of patients, and includes a number of conditions ranging from symptomatic uncomplicated diverticular disease and acute uncomplicated diverticulitis (AUD), to complicated forms of diverticulitis that occur in a small number (5%) of patients. Clinical management of diverticulitis is targeted towards common symptoms, such as acute pain in the left lower abdominal quadrant and signs of peritonitis, and is initially directed towards the prevention of progressive disease and the development of severe complications, such as abscesses or perforation.

The pathogenesis of the development of diverticula and associated DDC/diverticulitis is not fully understood. Outpouching of the colonic mucosa leading to diverticula is likely a multifactorial process caused by genetic aberrations, bowel wall tissue changes, environmental influences, enteric neuropathy with subsequent motility disturbances and dysbiotic microbiota. The development of inflammation in these diverticula leads to AUD. Longstanding hypotheses have suggested that impaction of faecal material causes low-grade inflammation, leading to abrasion of the mucosa, translocation of faecal microbiota to the mucosal connective tissue, resulting in acute injury of the mucosa with micro-perforation at the fundus of the diverticulum and peridiverticular inflammation. The role of bacteria from the enteric microbiota is not clearly understood, nonetheless, these hypotheses, together with typical clinical signs of bacterial inflammation, and the fear of progressing diverticulitis with perforation and peritonitis, have led to the general use of antibiotics in patients with diverticulitis over the past two decades. Early guidelines recommended hospitalisation, bowel rest and 7-10-day treatment with intravenous broad-spectrum antibiotics in patients with AUD, and this still remains the usual approach—a strategy reported to be successful in 85%-100% of patients. However, two randomised clinical trials and several observational studies have challenged the need for antibiotic treatment for patients with AUD. Based on these findings, and growing concerns regarding widespread bacterial resistance, a decline in the discovery of new antibiotics and multidrug resistance, several European guidelines no longer recommend routine antibiotic treatment for uncomplicated diverticulitis. A recent international consensus on diverticular disease noted that treatment of AUD without antibiotics is safe and effective, and is not associated with worse outcomes than treatment with antibiotics; both this consensus and the 2020 European Society of Coloproctology guidelines recommend that antibiotics only need to be considered in immunocompromised patients and those with comorbidities and/or sepsis. A recent high-quality systematic review confirmed the validity of this approach, but a subgroup analysis of randomised trials revealed that conservative treatment without antibiotics had a numerically higher chance of failure than antibiotic treatment. Moreover, patients included in the studies were given different antibiotics via varying routes of administration, therefore treatment heterogeneity could have affected the outcomes analyses. The study therefore suggested that further randomised trials are required to reach firmer conclusions on the efficacy and safety of non-antibiotic treatment in patients with uncomplicated diverticulitis. Both the American and German Gastroenterological Association (AGA, DGVS) guidelines conditionally recommend selective and individualised treatment on a case-by-case basis rather than routine use of antibiotics for AUD if no risk factors, such as immunosuppression, are present. It should be noted that these conservative recommendations are based on low-strength evidence from patients without complications; no placebo-controlled double-blind trial exists and the generally recommended 7- to 10-day medication periods are purely empirical.

Rifaximin has been the most studied antibiotic for DDC treatment, although a recent meta-analysis showed no proof of definite therapeutic effectiveness. Rifaximin is a derivative of the rifamycin subclass of broad-spectrum ansamycin antibiotics, and the anti-bacterial activity of rifamycin sodium against a broad-spectrum of microorganisms has been demonstrated. Non-absorbable antibiotics such as rifamycins have the potential for deleterious effects on beneficial gastrointestinal flora; however, new multi-matrix (MMX) formulation technology allows delivery directly inside the colon, with delayed and extended release to reduce side effects and improve efficacy. Although less than 1% of the orally administered rifamycin SV dose is absorbed after administration of Rifaximin SV-MMX®, the new tablet formulation specifically targets the colon by only releasing the active compound after reaching intestinal pH levels ≥7. Rifaximin tablets, given for 3 days at a total daily dose of 800 mg, was superior to placebo and non-inferior to ciprofloxacin for the oral treatment of travellers’ diarrhoea, with a lower risk of extended-spectrum beta-lactamase-producing Escherichia coli (ESBL-E. coli) acquisition.

This study of RIF-MMX was the first randomised, placebo-controlled, double-blind, double-dummy trial to investigate the therapeutic effects of a new antibiotic formulation that has similarities to rifaximin, the only hitherto-tested antibiotic group that has shown some promising effects in DDC, in patients with AUD.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a randomised, double-blind, double-dummy, multicentre, three-arm, comparative phase 2 clinical study comparing the efficacy and tolerability of 10 days’ oral treatment with RIF-MMX 400 mg twice daily (BID) (RIF-800) or RIF-MMX 600 mg three times a day (TID) (RIF-1800) vs placebo in patients with AUD. The two doses selected for investigation were based on recent clinical data from phase 2 (unpublished results) and phase three studies on RIF-MMX, in which 400 mg BID was the most effective and best-tolerated dose, and on rifaximin, for which the optimum dose was 550 mg TID for the treatment of irritable bowel syndrome.
Outpatients were enrolled between June 2013 and April 2017 at 28 gastroenterology centres in Germany, Hungary, Italy, Lithuania, Romania and Slovakia. The study was conducted in accordance with Good Clinical Practice, the Declaration of Helsinki and all applicable national laws, and was approved by independent ethics committees and institutional review boards from each of the centres. All patients provided written informed consent. The study protocol was registered at www.ClinicalTrials.gov (NCT01847664) and www.clinicaltrialsregister.eu (EudraCT 2012-003300-13). All authors had access to the study data and reviewed and approved the final manuscript.

2.2 | Patients

Eligible male and female patients aged 18-80 years qualified for outpatient treatment and had a diagnosis of left-sided AUD confirmed by ultrasonography and/or computed tomography (CT), with evidence of thickening of the wall (>5 mm) and/or confined pericolic inflammation of the left colon. Patients had at least one inflamed diverticulum of the left colon and left lower quadrant pain (LLQP), with a worst intensity of ≥4 on a visual analogue scale (VAS 0-10 cm) during the 24 hours before baseline. Additional inclusion criteria were C-reactive protein (CRP) > upper limit of normal (ULN) and ≤20 x ULN and/or leucocytosis (>ULN) at screening visit (only if due to acute diverticulitis), and indication of conservative therapy/management with no need for surgery or intervention.

Key exclusion criteria were existing complications of diverticulitis (diverticulitis associated with abscess, fistula, obstruction or perforation), right-sided diverticulitis, previous colonic surgery (except appendectomy, haemorrhoidectomy and endoscopic removal of polyps), chronic inflammatory bowel disease or celiac disease or presence of symptomatic organic disease of the gastrointestinal tract (with the exception of non-bleeding haemorrhoids or hiatal hernia). Additional exclusion criteria were inability to tolerate oral intake, stool positive for organisms causing bowel disease, use of antibiotic, antmycotic or antiviral treatment within 2 weeks prior to randomisation, use of 5-aminosalicylic acid (5-ASA, mesalazine, sulfasalazine) within 7 days prior to randomisation and use of glucocorticosteroids or immunosuppressants within 2 months prior to randomisation.

2.3 | Randomisation and masking

Eligible patients were randomly assigned by an interactive web-response system to one of three treatment groups in a 2:2:1 ratio: Group A: RIF-800, Group B: RIF-1800 and Group C: placebo. Randomisation was concealed by packaging the study medication using the double-dummy technique to guarantee blinding for all patients and investigators, as well as all other persons involved in the conduct of the study. To ensure blindness, patients were required to take three tablets of identical appearance (200 mg RIF-MMX and/or placebo) TID during the 10-day treatment period.

2.4 | Procedures

Rifaximin SV-MMX® (COSMO S.p.A., Lainate [MI], Italy) or placebo (200 mg tablets) were administered orally at doses of 400 mg BID (RIF-800) or 600 mg TID (RIF-1800).

The evaluation schedule comprised an up to 4-day screening phase and a 10-day double-blind treatment period, followed by a treatment-free 14-day follow-up phase and 32-day long-term follow-up phase. If patients’ signs or symptoms of AUD worsened disproportionately during the treatment phase, the study treatment could be stopped, and the patient could receive rescue therapy, but had to be withdrawn due to lack of efficacy from the treatment phase.

Efficacy and safety assessments started at baseline and were conducted at the interim visits at Day 3 and Day 7, and at the end of treatment visit at Day 10. Ultrasonography and/or CT were performed at screening (Day -4 to 0 before baseline). Follow-up visits with safety assessments and checks for recurrence of diverticulitis were conducted at Days 24 and 56. Patients were asked to keep a daily diary from screening until the first follow-up visit to document their intake of study medication and worst LLQP during the past 24 hours (0-10 cm VAS), together with other diverticulitis-related symptoms, number and condition of stools and ability to tolerate solid food. All concomitant medications taken from screening until the first follow-up visit were recorded, and clinical and laboratory adverse events were reported during the whole study period.

2.5 | Outcomes

The primary objective was to demonstrate the superiority of RIF-1800 and RIF-800 vs placebo; the primary endpoint was the rate of patients with treatment success at Day 10. The rates of treatment success for both RIF-MMX doses were also compared for exploratory purposes. Treatment success was achieved if all of the following criteria were fulfilled: absence of fever; adequate relief of LLQP (worst intensity <4 during the past 24 hours [VAS]); no pain medication taken within the past 48 hours except for chronic low-dose acetylsalicylic acid ≤ 100 mg/d for reasons other than pain; absence of leucocytosis (leucocytes ≤ ULN); and CRP ≤ULN or ≥50% improvement compared with baseline, each on the day of visit. Further criteria comprised: no complications of acute diverticulitis and no need for extra antimicrobial treatment, surgical intervention or hospitalisation due to acute diverticulitis, each up to the day of visit. Treatment success was not achieved if at least one of these criteria was violated.

The key secondary endpoint was the rate of complete treatment success at Days 3, 7 and 10, as defined for the primary endpoint, except that the CRP ≤ ULN criterion was an absolute requirement (≥50% improvement compared with baseline was not acceptable). Further secondary endpoints included the rate of patients with surgical intervention, antimicrobial treatment and hospitalisation, each due to acute diverticulitis; and the rate of patients who received...
rescue therapy, course of CRP from baseline until visit Day 10 and course of intensity of LLQP (0-10 cm VAS).

An exploratory post-hoc analysis was performed by stratifying treatment success and complete treatment success at Days 3, 7, 10 and Day 10 last observation carried forward (LOCF) by duration of present attack of AUD ≤ 3 days vs >3 days (3 days is the median duration of present attack in the intention-to-treat [ITT] population for the RIF-800 and placebo groups; Table 1), and by number of previous AUD episodes (≥2 previous episodes or ≤1 previous episode).

All clinical efficacy analyses were performed for the ITT population and for the per-protocol (PP) population. The primary analysis set comprised the ITT population, which included all patients who received ≥1 dose of study medication. Major protocol violations leading to exclusion from the PP set included violations of major

**TABLE 1** Patient demographics and baseline characteristics (ITT population)

|                          | RIF-800  | RIF-1800 | Placebo  |
|--------------------------|----------|----------|----------|
| (n = 82)                 | (n = 79) | (n = 40) |
| Female gender, n (%)     | 44 (53.7)| 49 (62.0)| 27 (67.5) |
| Age (y), mean (SD)       | 59.7 (10.7)| 58.4 (11.1)| 56.8 (13.8) |
| BMI (kg/m^2), mean (SD)  | 29.3 (4.4) | 29.3 (5.8) | 28.4 (5.2) |
| Worst left lower quadrant pain, a mean (SD) | 5.91 (2.1) | 5.4 (2.1) | 5.5 (2.2) |
| CRP (mg/L), mean (SD)    | 44.6 (40.5) | 35.0 (36.9) | 43.1 (44.5) |
| Signs of inflammation of colonic wall (US/CT findings), b n (%) | 81 (98.8) | 78 (98.7) | 40 (100.0) |
| Detection of ≥1 individual inflamed diverticulum (US/CT findings), b n (%) | 81 (98.8) | 79 (100.0) | 40 (100.0) |
| No presence of complications (US/CT findings), b n (%) | 82 (100.0) | 79 (100.0) | 40 (100.0) |
| Symptoms of acute episode, c n (%) | | | |
| Left lower quadrant pain | 80 (97.6) | 79 (100.0) | 40 (100.0) |
| CRP > ULN                | 77 (93.9) | 75 (94.9) | 37 (92.5) |
| Bloating                 | 37 (45.1) | 33 (41.8) | 19 (47.5) |
| Leucocytes > ULN         | 32 (39.0) | 37 (46.8) | 16 (40.0) |
| Diarrhoea                | 17 (20.7) | 17 (21.5) | 7 (17.5) |
| Constipation             | 15 (18.3) | 17 (21.5) | 6 (15.0) |
| Nausea                   | 13 (15.9) | 12 (15.2) | 12 (30.0) |
| Faecal urgency           | 20 (24.4) | 12 (15.2) | 2 (5.0) |
| Faecal tenesmus          | 13 (15.9) | 16 (20.3) | 4 (10.0) |
| Lethargy                 | 12 (14.6) | 6 (7.6) | 9 (22.5) |
| Vomiting                 | 7 (8.5) | 6 (7.6) | 3 (7.5) |
| Fever > 38°C             | 5 (6.1) | 7 (8.9) | 0 (0) |
| Other                    | 2 (2.4) | 4 (5.1) | 2 (5.0) |
| Duration of present attack of uncomplicated diverticulitis (d), median (range) | 3.00 (0.0-202.0) | 4.50 (0.0-50.0) | 3.00 (0.0-32.0) |
| Number of previous acute episodes of diverticulitis, n (%) | | | |
| 0                        | 49 (59.8) | 47 (59.5) | 26 (65.0) |
| 1                        | 20 (24.4) | 17 (21.5) | 6 (15.0) |
| ≥2                       | 12 (14.6) | 15 (19.0) | 7 (17.5) |
| Number of previous episodes of acute symptomatic diverticular disease, n (%) | | | |
| 0                        | 71 (86.6) | 67 (84.8) | 31 (77.5) |
| 1                        | 7 (8.5) | 9 (11.4) | 4 (10.0) |
| ≥2                       | 3 (3.6) | 1 (1.3) | 4 (10.0) |

Note: RIF-800, RIF-MMX 400 mg twice daily; RIF-1800, RIF-MMX 600 mg three times daily.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; CT, computed tomography; ITT, intention-to-treat; RIF-MMX, Rifamycin SV multilayer matrix; SD, standard deviation; ULN, upper limit of normal; US, ultrasonography; VAS, visual analogue scale.

aPain intensity over the past 24 h (0 – 10 cm VAS).

bResults are based on US or CT. If a valid value is available from both examinations, the CT result is presented.

cPresented in order of overall incidence.
inclusion criteria, use of prohibited concomitant medication, administration of study medication for less than 3 days, end of treatment/wrathdrawal visit more than 3 days after last study medication intake, insufficient compliance with respect to intake of study medication, unavailability of post-baseline efficacy data under treatment with study medication and premature discontinuation from treatment—unless the reason for discontinuation was lack of efficacy, intolerable adverse events with at least possible causal relationship with the study medication or an intolerable adverse event that was a deterioration of the study disease. All safety data were analysed in the safety population (patients who received at least one dose of study medication and had at least one follow-up safety variable value).

2.6 | Statistical analysis

Assuming a treatment success rate of 90% in the RIF-800 and RIF-1800 groups, and of 75% in the placebo group, the statistical power of the test procedure was 80%, with a sample size of 375 patients in the ITT analysis.

The study was a three-stage group-sequential adaptive design, with possible sample size adjustment or early stopping of the study for efficacy, futility or safety after the interim analyses. The first interim analysis was planned after the observation of 185 evaluable ITT patients and the second interim analysis after a total of 280 ITT patients, both conducted by an independent data monitoring.
committee (IDMC), established by the sponsor prior to the interim analysis.

In order to adjust for multiple testing, the hypotheses were tested in an a priori order. Confirmative testing of the RIF-800 group vs the placebo group was only possible if superiority was proved for the RIF-1800 group against the placebo group. This order was specified during protocol development as a dose linearity was assumed. For hypothesis testing of the primary endpoint, the overall (experiment-wise) type I error rate was $\alpha = 0.025$ (one-sided). All other statistical tests were performed two-sided with a significance level of $\alpha = 0.05$ on an exploratory basis. A sensitivity analysis was carried out using a LOCF approach.

Analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC, USA) and ADDPLAN®, version 6.1.1 (licensed by ADDPLAN, Inc. an ICON Clinical Research, LLC company) and according to the ITT principle.

2.7 | Role of the funding source

The study sponsor provided the study drug and collaborated with the investigators on protocol design, data collection and interpretation. An independent data monitoring committee oversaw the study integrity and patient safety. The coordinating investigators (WK) and lead authors (TN, RG) had final responsibility for the report content and decision to submit for publication. The sponsor funded writing assistance.

3 | RESULTS

3.1 | Patients

Overall, 300 patients with AUD were screened for enrolment. The study was stopped for futility upon recommendation from the IDMC after the first interim analysis (185 ITT patients) and it was also recommended to suspend further patient recruitment. The decision for futility was based on comparable results between the high-dose RIF-1800 group and placebo group and no significant difference in the primary endpoint of the rate of patients with treatment success at Day 10, thus preventing confirmatory testing of the low-dose RIF-800 group vs placebo. Recruitment continued during the interim analysis and a total of 204 patients were randomly assigned to the three treatment groups (RIF-800, RIF-1800 and placebo; Figure 1). Three of these patients did not receive study medication and the final analysis was performed on 201 patients in the ITT group and 143 patients in the PP group (58 patients in the ITT population were excluded from the PP group due to relevant protocol violations). The analysis of safety was performed on a total of 199 randomised patients who received study medication and had at least one follow-up value for the safety variables. In total, 26 patients terminated the treatment phase prematurely, most commonly due to lack of cooperation from the patients, lack of efficacy and intolerable adverse events (Figure 1).

Demographic and baseline anamnestic parameters were generally comparable across the treatment groups; however, some imbalances in gender distribution, CRP values, symptoms of the present acute episode and duration of the present AUD attack were observed (Table 1). The majority of patients had not previously experienced an acute episode of AUD or symptomatic uncomplicated diverticular disease without inflammation (Table 1). Mean and median baseline CRP values were lower in the RIF-1800 group than the RIF-800 and placebo groups.

3.2 | Clinical efficacy

3.2.1 | Treatment success

The primary endpoint of treatment success at Day 10 occurred more frequently in the RIF-800 group (62.2%) than in the RIF-1800 (49.4%) or placebo groups (47.5%) (Figure 2A). While treatment success rates for RIF-1800 and placebo were comparable (rate difference 1.9% [95% CI -17.1, 20.9; $P = 0.42$]), the rate of patients with treatment success between RIF-800 and placebo showed an absolute difference of 14.7% (95% CI -4.0, 33.4) at Day 10 but was slightly short of statistical significance ($P = 0.06$). In general, when comparing the two active treatment groups, a trend for higher efficacy with the lower RIF-800 dose compared with the higher RIF-1800 dose was observed. Similar efficacy trends were seen amongst the PP population. Treatment success rates at Day 3 and Day 7 (secondary endpoint) were similar for RIF-800 and placebo (Figure 2A).

3.2.2 | Complete treatment success

Both RIF-800 and RIF-1800 reached significantly ($P < 0.05$) higher complete treatment success rates (11.0% and 12.7%, respectively) at Day 3 compared with placebo (0%) (Figure 2B). Complete treatment success rates for later visits were not significantly different between the treatment groups, although again, the RIF-800 group performed numerically better compared with the RIF-1800 group (Figure 2B).

3.2.3 | Exploratory post-hoc analysis by number of previous episodes of AUD

There was a trend towards generally lower rates of treatment success and complete treatment success in the placebo group in patients with ≥2 previous episodes of AUD compared with those with ≤1 previous episode, in contrast to the RIF-800 and RIF-1800 groups, wherein rates were comparable. For the primary endpoint of Day-10 treatment success, there was a higher treatment success
rate in the RIF-800 and RIF-1800 groups compared with the placebo group among patients with ≥2 previous episodes of AUD (RIF-800: 66.7% vs 14.3% for placebo, \( P = 0.06 \); RIF-1800: 60% vs 14.3% for placebo, \( P = 0.07 \)), in contrast to patients with ≤1 previous episode, wherein rates in the RIF-800 and RIF-1800 groups were generally comparable with the placebo group (Table S1).
FIGURE 3  Rate of patients with treatment success (A) or complete treatment success (B) with symptom duration of present attack longer than 3 days on Day 3/7/10 and Day 10 (LOCF). All P-values are compared with placebo. RIF-800, RIF-MMX 400 mg twice daily; RIF-1800, RIF-MMX 600 mg three times daily. LOCF, last observation carried forward; RIF-MMX, Rifamycin SV multi-matrix.
For complete treatment success, the difference between the placebo group and the RIF-800 or RIF-1800 group was more pronounced in patients with ≥2 previous episodes of AUD at all visits compared with those with ≤1 previous episode of AUD. At Day 10, the difference in complete treatment success rates between the RIF-800 group and the placebo group was 52.4% (66.7% vs 14.3% respectively $P = 0.06$) and between the RIF-1800 group and the placebo group was 41% (53.3% vs 14.3% respectively $P = 0.16$) (Table S1).
Exploratory post-hoc analysis by duration of present attack

Exploratory post-hoc analysis stratifying treatment success and complete treatment success by duration of present attack (≤3 days or >3 days of AUD) showed that patients with more than 3 days of symptoms benefited most from RIF-MMX treatment (Figure S1). For patients with symptom duration >3 days, both the rate of treatment success (60.0%) (Figure 3A) and complete treatment success (53.3%) (Figure 3B) at Day 10 was significantly higher in the RIF-800 group compared with the placebo group (*P* = 0.02 and *P* = 0.01, respectively; 16.7% and 8.3%, respectively). Again, there was a trend for higher efficacy with the lower RIF-800 dose compared with the higher RIF-1800 dose.

### Other secondary efficacy variables

In all three treatment groups, a continuous increase in the rate of patients with CRP ≤ ULN and a continuous decrease in the rate of patients with LLQP was observed from baseline during the course of the study (Figure 4A,B). In general, mean CRP and LLQP values in all three treatment groups decreased significantly from baseline.
to Day 10, but without significant differences (two-sided t-test) between the three treatment groups (Table 1). The rate of patients with CRP ≤ ULN at Day 3 was numerically higher in the RIF-800 group (22.0%) and RIF-1800 group (27.8%) than in the placebo group (12.5%), reflecting the complete treatment success efficacy results. At Day 7, the difference was less pronounced, and at visit Day 10 and Day 10 (LOCF), results from the placebo group were comparable to the results from the RIF-800 group and slightly higher than the results from the RIF-1800 group (Figure 1A). Mean baseline LLQP was slightly higher in the RIF-800 group than in the other two groups and the reduction from baseline until Day 10 was highest in the RIF-800 group (Figure 4B; Table 2), but without clear differences between groups.

The majority of patients did not receive rescue therapy due to acute diverticulitis; the rate of patients with rescue therapy was highest in the RIF-800 group, with no statistical significance (Table 2). Correspondingly, most patients were not hospitalised due to acute diverticulitis and did not experience complicated diverticulitis (Table 2). No surgical interventions were reported until visit Day 10 (one patient treated with RIF-1800 received a surgical intervention for acute diverticulitis during follow up).

During the follow-up phase (until Week 8), the rate of recurrent diverticulitis was low (5.1% in the RIF-1800 group, 2.5% in the placebo group and 0% in the RIF-800 group). No cases of complicated diverticulitis occurred during this phase.

### 3.3 Safety

Treatment-emergent adverse events occurred in 33.3% of patients in the RIF-800 group, in 35.9% of patients in the RIF-1800 group and in 25.0% of patients in the placebo group (Table 3). Adverse drug reactions were reported in 6/81 patients (7.4%) taking RIF-800, 7/78 patients (9.0%) taking RIF-1800 and 5/40 patients (12.5%) taking placebo. Gastrointestinal disorders were the most commonly reported adverse drug reactions in all three treatment groups.

Serious adverse events (SAEs) were reported in 3/81 patients (3.7%) taking RIF-800, 5/78 patients (6.4%) taking RIF-1800 and no patients (0%) taking placebo. Treatment-emergent SAEs were reported in 1/81 patients (1.2%) taking RIF-800, 1/78 patients (1.3%) taking RIF-1800 and no patients (0%) taking placebo. All (except one) SAEs were assessed as either not related or unlikely to be related to RIF-MMX; the one SAE was Clostridium difficile colitis, occurring 41 days post treatment in the RIF-1800 group, which was an unexpected serious adverse reaction considered as possibly related to treatment. A 74-year-old patient in the RIF-800 group died during the course of this study due to a cerebrovascular accident that occurred about 4 weeks post treatment; this event was not considered as study drug related by the investigator.

Treatment-emergent adverse events led to study drug discontinuation in 2/81 patients (2.5%) in the RIF-800 group, 3/78 patients (3.8%) in the RIF-1800 group and no patients (0%) in the placebo group.

### 4 DISCUSSION

To our knowledge, this study is the first prospective, randomised, double-blind, double-dummy, placebo-controlled clinical study evaluating antibiotic treatment for AUD. The trial compared an oral 10-day treatment with RIF-MMX 400 mg BID, RIF-MMX 600 mg TID and placebo in an outpatient setting.

In a previously reported multicentre, randomised, open-label study in patients with AUD, without predefined antibiotic use in the control arm, antibiotic treatment did not accelerate recovery nor prevent complications or recurrence, and was recommended for the treatment of complicated diverticulitis only. In another randomised study without a control arm that evaluated observational vs antibiotic treatment of CT-proven primary AUD, observational treatment without antibiotics did not prolong recovery and therefore a non-antibiotic approach was suggested as an appropriate option in patients with uncomplicated disease. In order to evaluate risk factors in those patients who experienced non-antibiotic treatment failure, a retrospective cohort study of 565 patients with CT-proven AUD who were initially treated with antibiotics was carried out (30-day follow up). In a multivariable analysis of the study, patients with AUD and a CRP level >170 mg/L were found to be at higher risk for non-antibiotic treatment failure. Despite such studies to identify risk factors that may help clinical decision making, the impact of acute episodes of diverticulitis on patients’ quality of life renders observational, non-interventional treatment decisions difficult for both patients and physicians. Commonly experienced acute symptoms of significant abdominal pain and tenderness make early treatment success an important goal. In addition, anxiety or depression related to these symptoms and the potential for complications or recurrence, especially in patients with a history of diverticular disease, has been shown to have a detrimental effect on patients’ quality of life both during and after attacks. Taken together, these findings support the need for new approaches that may lead to more rapid resolution of acute episodes of diverticulitis.

Accordingly, the study reported here has provided clinical evidence towards the generation of a new treatment strategy for patients with AUD, based on early antibiotic treatment to resolve acute episodes of the disease and improve quality of life. The primary endpoint of predefined treatment success in this study fell slightly short of statistical significance (P = 0.06), but clinical benefit was evident, with a trend for a higher rate of antibiotic treatment success with RIF-800 vs placebo, and the secondary endpoint of complete treatment success at Day 3 was met for both treatment groups. In addition, an exploratory analysis showed significance for treatment success and complete treatment success with RIF-800 in patients with longer duration of AUD. Overall, treatment with RIF-MMX trended to demonstrate therapeutic superiority over placebo, and achieved complete treatment success faster than placebo, with the most pronounced effect confirmed at Day 3.

Patients with more than 3 days of symptoms of AUD benefited most from antibiotic treatment, and the lower dose of RIF-MMX...
(RIF-800) trended to be more effective than the higher dose (RIF-1800). Nonetheless, the tendency for lower efficacy of the high RIF-1800 dose (comparable to placebo) is an unexpected finding that could potentially be due to the deleterious effects of higher rifamycin doses on the gut microbiome, including the saprophytic beneficial flora, that may lead to fewer patients achieving complete treatment success. Overall, RIF-800 or RIF-1800 were well tolerated by the vast majority of patients in this study, and the safety analyses did not raise any concerns for a 10-day oral treatment in patients with AUD.

In line with published recommendations, a 10-day treatment period was selected for this study, and the primary efficacy variable was also evaluated at Day 10. A 94% success rate has been reported in patients with AUD who received antibiotic treatment for 10-13 days,\(^{31}\) however, it remains unclear whether 10-day antibiotic treatment is necessary in this indication and also whether efficacy evaluation at Day 10 is the most appropriate timepoint. Indeed, data from this study showed that the rate of patients in the placebo group reaching complete treatment success increased from Day 3 to Day 10, and there was no significant difference between the three study groups at Day 10. These data suggest that AUD may be a self-limiting disease that does not necessarily require antibiotic treatment in the majority of patients. Furthermore, shorter courses of antibiotic therapy are increasingly common due to diseases associated with antibiotic resistance,\(^{32}\) and a reduced treatment period of 1-3 days could be considered. This strategy may lead to a new treatment goal of a faster disease resolution in patients with AUD and suggests that future studies should focus on optimal time to analyses. A previous randomised (non-placebo controlled) study of the antibiotic ertapenem reported that short-term (4-day) therapy was as effective as standard (7-day) therapy for the treatment for uncomplicated sigmoid diverticulitis,\(^{33}\) and seems to support the concept that a short-term course of antibiotics might be adequate for AUD. Indeed, the lack of an approved endpoint for clinical trials in this indication has confounded comparative studies, and our results suggest that complete treatment success may be a more appropriate endpoint than treatment success. Accordingly, this study showed that both RIF-MMX groups reached significantly (\(P < 0.05\)) higher complete treatment success rates (11.0% and 12.7%, respectively) at Day 3 compared with placebo (0%). Interestingly, this was not the case at Day 3 when using the primary efficacy variable of treatment success. The contrasting rates of treatment success and complete treatment success (for the latter, \(\text{CRP} \leq \text{ULN} \) had to be fulfilled) reflect that while many patients in the placebo group achieved a CRP reduction of >50%, they still remained above the ULN.

Patients in the placebo group with \(\geq 2\) previous episodes of AUD tended to show lower rates of treatment success and complete treatment success than those with \(\leq 1\) previous episode of AUD. In contrast, treatment success and complete treatment success rates in the RIF-800 and RIF-1800 groups were comparable, irrespective of the number of previous episodes of AUD. Patients with a longer duration of their current AUD attack trended to show higher rates of complete treatment success when treated with RIF-MMX at Day 3, Day 7 and Day 10 compared with placebo, showing statistical significance (\(P = 0.01\)) at Day 10 for RIF-800. These data suggest that AUD may be a recurrent rather than a self-limiting disease for a specific population of patients. Therefore, for future studies, it will be important to determine which patients benefit most from antibiotic treatment based on disease history, clinical presentation and biomarker (eg CRP) evaluation.

In conclusion, antibiotic treatment with RIF-MMX trended to demonstrate therapeutic superiority over placebo in AUD and near-statistical significance. RIF-MMX more rapidly achieved complete treatment success compared with placebo, with the most pronounced effect seen early in the treatment course at Day 3 as well as in patients with a recurrent disease pattern. RIF-MMX was well tolerated, and the results from this study suggest that patients with a recurrent disease pattern or a prolonged duration of AUD symptoms might benefit from a short course of antibiotic treatment with the lower RIF-800 dose. Moreover, a shorter treatment period of 3 days may further decrease the risk of antibiotic resistance.

This study provided proof-of-concept of the efficacy of low doses of RIF-MMX given for a short period of time and/or for specific patient populations (eg patients with longer duration of disease symptoms, significant pain early in the disease and/or elevated CRP). Short-duration antibiotic treatment for symptomatic acute-phase disease, followed by observation, may be a potential future therapeutic strategy. Randomised, double-blind clinical studies based on the clinical endpoints identified in this study are required to confirm these findings. Antibiotics for AUD may not be a ‘yes or no’ decision, and the therapeutic advantages must be balanced vs risk in individual patients.

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**CONFLICT OF INTERESTS**

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AUTHORSHIP
Guarantor of the article: Wolfgang Kruis.

Author contributions: Wolfgang Kruis contributed to development of the study protocol, patient recruitment, data collection, data analysis/interpretation, manuscript preparation, review and final approval of the manuscript. Tomas Poškus, Günther Böhm, Ivan Bunganic, István Rácz, Ovidiu Fratila and Giovanni Barbara contributed to patient recruitment and data collection, review and final approval of the manuscript. Sarah Wehrum contributed to manuscript preparation, review and final approval of the manuscript. Tanju Nacak and Roland Greinwald contributed to development of the study protocol, data analysis/interpretation, manuscript preparation, review and final approval of the manuscript. All authors have approved the final version of the article, including the authorship list.

DATA AVAILABILITY STATEMENT
Data collected for the study, including individual participant data and a data dictionary defining each field in the set, will not be made available to others, as per ethical committee agreements.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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