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SUMMARY

Background
Aminosalicylates are first-choice treatment for mild-to-moderately active ulcerative colitis (UC); however, multi-dosing regimens are inconvenient.

Aim
To compare the efficacy and safety of once- (OD) vs. twice- (BD) daily prolonged-release mesalazine (Pentasa, Ferring, Saint-Prex, Switzerland) for active mild-to-moderate UC in a non-inferiority study.

Methods
Eligible patients (n = 206) were randomised to 8 weeks of mesalazine (4 g/day), either OD with two sachets of 2 g mesalazine granules in the morning (n = 102) or BD with one 2 g sachet in the morning and one in the evening (n = 104). Patients also received 4 weeks of mesalazine enema 1 g/day. Disease activity was assessed at randomisation, weeks 4, 8 and 12 using the UC Disease Activity Index (UC-DAI). Clinical and endoscopic remission (primary endpoint) was assessed after 8 weeks. Patients recorded stool frequency and rectal bleeding in a daily diary.

Results
The primary endpoint, non-inferiority in clinical and endoscopic remission with OD vs. BD mesalazine at 8 weeks, was met (intent-to-treat population: 52.1% vs. 41.8%, respectively, 95% confidence interval −3.4, 24.1; P = 0.14). Improvement of UC-DAI score (92% vs. 79%; P = 0.01) and mucosal healing (87.5% vs. 71.1%; P = 0.007) were significantly better, time to remission significantly shorter (26 vs. 28 days; P = 0.04) and safety similar with OD vs. BD dosing.

Conclusions
When combined with mesalazine enema, prolonged-release mesalazine once-daily 4 g is as effective and well tolerated as 2 g twice-daily for inducing remission in patients with mild-to-moderately active ulcerative colitis (Clinicaltrials.gov: NCT00737789).

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon and rectum, characterised by recurrent disease flares and periods of remission (quiescence). In addition to their use in maintaining remission, aminosalicylates are also the current standard of care for inducing remission in mild-to-moderate active UC.[1, 2] Rectal (topical) administration is the optimal treatment choice for proctitis and left-sided colitis, whereas oral treatment is chosen for mild-to-moderate extended disease. Mesalazine is an aminosalicylate that comes in both oral (tablet, sachets) and topical forms (liquid or foam suspensions, gels, suppositories), which means that it can be used for the range of disease presentations. Oral mesalazine formulations have a delayed-release mechanism through the use of a pH-dependent or ethylcellulose coating. These preparations do not dissolve in the stomach, but start to release mesalazine in the small bowel, with the majority of drug released into the colon, thereby targeting the whole colon.

The conventional dosing schedule used for oral mesalazine is a minimum of twice daily (BD). This practice of divided dosing stems from a desire to reduce the toxicity and side effects that were originally associated with sulfasalazine therapy. Newer mesalazine agents are better tolerated and when delayed-release mesalazine is given once daily (OD), urinary, faecal and rectal tissue concentrations of the drug are equivalent to those seen with divided dosing schedules.[3] In addition, 4 g oral ethyl-cellulose-coated mesalazine given OD has been shown to be bioequivalent to a BD regimen after single or repeated administration.[4]

Adherence to oral mesalazine among patients with quiescent UC is poor.[5, 6] Part of the explanation for this poor adherence may be inconvenient dosing regimens.[7] Reducing the number of doses is a simple way to fit with patient preferences when prescribing mesalazine, and this has been shown to be effective and safe in active UC with some formulations of mesalazine.[8–10]

Prolonged-release mesalazine (Pentasa, Ferring, Saint-Prex, Switzerland) is available as an oral formulation (tablets or granule sachets) and has been shown to be effective in mild-to-moderate active UC at doses of 4 g/day for achieving remission.[11, 12] At this dose, remission from active disease can be achieved in 8 weeks. For optimal therapeutic benefit, the combined use of oral and topical mesalazine is recommended for active mild-to-moderate UC, as indicated in the European Crohn's and Colitis Organisation guidelines.[2]

This study was a multicentre, controlled, randomised, investigator-blinded, comparative study designed to investigate the non-inferiority of OD vs. BD administration of oral prolonged-release mesalazine granules for inducing clinical and endoscopic remission, when combined with mesalazine enema, in patients with mild-to-moderate, active UC.

PATIENTS AND METHODS

The trial protocol was approved by all relevant ethics committees, and was carried out in accordance with the principles of Good Clinical Practice, the Declaration of Helsinki and all applicable laws and regulations related to clinical trials in the participating countries. All patients provided written informed consent prior to any study-related procedure (clinicaltrials.gov identifier: NCT00737789).

Patients

Male and female patients $\geq$18 years of age were eligible to participate in the trial if they had newly diagnosed or relapsing mild-to-moderate UC, with disease extension beyond the rectum ($\geq$12–18 cm from the anorectal junction). Patients must have had at least one total colonoscopy in the past 5 years and have an UC Disease Activity Index (DAI) score of 3–8 within 15 days prior to study entry.

Patients were excluded if they had undergone previous colonic surgery, failed to respond to steroids, or failed to achieve remission with rectal or oral mesalazine therapy within the year prior to the study. Patients in current relapse for more than 6 weeks were excluded, as were patients with severe or fulminant UC, evidence of other forms of inflammatory bowel disease, infectious disease, or allergies to acetylsalicylic acid or salicylate derivatives. Additional exclusion criteria included significant hepatic or renal function abnormalities or abnormal blood cell counts, pregnancy or lactation, or history of another disease that might interfere with participation in the study. Prohibited or non-allowed concomitant medication without a washout period included aminosalicylates at a higher dose than permitted for maintenance treatment, oral or rectal corticosteroids, loperamide and other anti-diarrhoeal agents, oral or rectal nonsteroidal anti-inflammatory drugs (other than cardioprotective low-dose acetylsalicylic acid), antibiotics and immunosuppressives (other than azathioprine or mercaptopurine). Washout periods of varying lengths (1 week–3 months depending on medication) were required prior to study entry. Oral maintenance with azathioprine or mercaptopurine was permitted if this had been used at stable doses for at least 6 months prior to study entry.

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Study design

The MOTUS (Mesalazine granules 4 g per day Once daily versus 4 g per day in Two divided doses in patients with active Ulcerative colitiS) trial was a phase IIIb, randomised, controlled, investigator-blinded trial carried out at 44 centres in four European countries (France, the United Kingdom, Belgium and the Netherlands) between November 2008 and June 2010. Patients were randomised to receive 8 weeks of mesalazine [Pentasa (Ferring), 4 g/day] as either OD treatment with two sachets of 2 g mesalazine granules taken at the same time in the morning or BD treatment with one 2 g sachet taken in the morning and another in the evening. Patients were randomised centrally via a computer-generated randomisation system. When remission was achieved at week 8, patients were given a further 4 weeks of oral maintenance mesalazine, 2 g sachet OD (week 8 to week 12). If remission was not achieved, treatment was given at the investigator's discretion. All patients also received a 100-mL enema at bedtime containing 1 g mesalazine for the initial 4 weeks of the study. To maintain the investigator-blind trial design, sealed treatment boxes were identical in size and weight, and contained written instruction about the dosing arm to which the patient was assigned; investigators were unaware of this information. As an additional measure, patients were instructed to avoid giving information about the dosing regimen they were using. Disease activity was assessed using the UC-DAI score, measured at randomisation and week 8.[12, 13] The UC-DAI score is the total of four parameters, each scoring between 0 and 3: (i) stool frequency (0, normal; 1, 1–2 stools/day more than normal; 2, 3–4 stools/day more than normal; 3, >4 stools/day more than normal, based on average of last 3 days), (ii) rectal bleeding (0, no traces of blood; 1, traces of blood; 2, frank blood; 3, mainly blood, using most severe episode in last 3 days), (iii) mucosa appearance based on sigmoidoscopy (0, normal; 1, erythema, reduced capillary network, mild friability, minimal granularity; 2, friability, marked erythema, no vascularisation, erosions, pus; 3, ulcers, spontaneous bleeding), and (iv) the physician's global assessment (0, no active disease; 1, mild disease; 2, moderate disease; 3, severe disease).[12] Endoscopic findings were also graded according to the Rachmilewitz endoscopic index, which considers granulation, vascular pattern, vulnerability of the mucosa and mucosal damage.[14] An abbreviated UC-DAI score without endoscopic sub-score was used at week 4 (visit 2) and week 12. Patients recorded stool frequency and rectal bleeding in a daily diary.

Endpoints

The primary endpoint was the percentage of patients in clinical and endoscopic remission after 8 weeks (defined as UC-DAI score ≤ 1). Secondary endpoints included complete remission at week 8 (clinical and endoscopic UC-DAI = 0), clinical and endoscopic improvement at week 8 (decrease in UC-DAI by at least 2 points), and clinical remission at weeks 4, 8 and 12, determined by normal stool frequency, no bloody stools and no active disease by physician's assessment. Additional secondary endpoints included time to remission (according to the patient's diary with normal stool frequency and cessation of bleeding; estimated using Kaplan–Meier methodology) and mucosal healing at 8 weeks (defined as an UC-DAI endoscopic sub-score of 0 or 1, or alternatively a Rachmilewitz endoscopic index of <4). Compliance with study medication was measured as (no. of sachets or enemas dispensed − no. of sachets or enemas returned) × 100/2 × duration of treatment days. Global patient's acceptability was assessed using a 100-mm visual analogue scale, delimited from much worse (0%) to very much improved (100%). Safety assessments included adverse event (AE) reporting, laboratory tests, vital signs and physical examination. AEs were coded according to the Medical Dictionary for Regulatory Activities, version 13.0.

Sample size determination and statistical analyses

It was determined that a total target sample size of 179 valid patients per treatment arm would provide 80% simultaneous power at a one-sided alpha-level of 0.025 to detect a clinically relevant difference of 15% between dosing regimens (based on a remission rate of 64% in the control group, as previously obtained with the same design).[12] To allow for non-evaluable patients, a sample size of 199 patients per treatment group was chosen.

Analysis of the primary endpoint is presented for the intent-to-treat (ITT) population [all randomised patients who received at least one dose of study medication, evaluated for last observation carried forward (LOCF) and observed cases (OC)] and the per-protocol (PP) population (all ITT patients without any major protocol deviation, evaluated for LOCF and OC). Secondary endpoints are presented for the ITT population. Missing data were accounted for using the LOCF method for the ITT population. This was applied separately to each sub-score of the UC-DAI; no missing data were imputed for the PP population.

Analyses were performed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA), where all tests were two-sided with an alpha-level of 0.05. Analysis of

variance was used to assess responses for efficacy endpoints and normative qualitative variables were analysed using a Cochran-Mantel-Haenszel (CMH) Chi-squared test. Non-inferiority was evaluated by calculating the 95% two-sided confidence interval (CI) of the difference in remission rates between the two dosing arms. If the lower end of the CI was greater than −15%, then the OD regimen was declared non-inferior to the BD regimen. If non-inferiority was proven, superiority was tested using the CMH test and the weighted estimates given.

RESULTS

Demographic and baseline patient characteristics are shown in Table 1. The percentage of patients with left-sided or distal UC (>80%) and the severity of flare were similar in both groups. Due to difficulties in patient recruitment, only 206 patients were randomised to treatment (despite extension of the study by 6 months and inclusion of 10 additional centres in France) (Figure 1). A total of 102 and 104 patients receiving OD and BD oral mesalazine, respectively, were entered into the trial. For the OD arm, 101 patients (99%) comprised the ITT population and 79 patients (77%) comprised the PP population. For the BD arm, 101 patients (97%) comprised the ITT population and 77 patients (74%) comprised the PP population (Figure 1). A total of 16 patients from the OD group and 17 patients from the BD group withdrew from the study prematurely (12 OD, 13 BD before week 8) for a number of reasons, including AEs (OD, $n = 4$; BD, $n = 4$), worsening of disease (OD, $n = 1$; BD, $n = 2$), withdrawal of consent (OD, $n = 4$; BD, $n = 5$), inadequate response (OD, $n = 2$; BD, $n = 1$) or lost to follow-up (OD, $n = 1$; BD, $n = 1$).

Table 1 | Demographic and patient baseline characteristics

n	OD (*n* = 102)	BD (*n* = 104)
Male/female, *n* (%)	58 (57)/44 (43)	52 (50)/52 (50)
Median age, years (range)	40.5 (18–75)	43.5 (18–82)
Smoking status, *n* (%)		
Current smoker	15 (15)	11 (11)
Ex-smoker	39 (38)	46 (44)
Never smoked	48 (47)	47 (45)
Median time between diagnosis and inclusion, months (range)	37 (1–487)	53 (1–529)
Median number of previous episodes (range)	1 (0–28)	2 (0–30)
Median time from the onset of current episode to inclusion, days (range)	14 (5–30)	14 (6–27)
Recurrent episodes: yes/no/missing, *n* (%)	61 (60)/40 (39)/1 (1)	71 (68)/33 (32)/0 (0)
Disease extension, *n* (%)		
Left-sided UC, including distal UC*	83 (81)	88 (85)
Pancolitis, including extensive UC†	19 (19)	16 (15)
Median UC-DAI score at baseline (range)	7 (3–8)	6 (3–8)
Concomitant immunosuppressor, *n* (%)	1 (1)	3 (3)

BD, twice-daily; DAI, disease activity index; OD, once-daily; UC, ulcerative colitis.

* Corresponding to Montreal classification E2.

† Corresponding to Montreal classification E3.

Primary endpoint

At week 8, 52.1% of patients in the ITT OD group and 41.8% of patients in the BD group were in clinical and endoscopic remission (UC-DAI score ≤ 1). As the lower limit of the 95% CI was between −15% and 0% (−3.4, 24.1), the trial achieved its primary endpoint of non-inferiority of OD vs. BD dosing of mesalazine (Figure 2). Non-inferiority was also shown in the PP population (61.0% vs. 48.3%, 95% CI: −2.7, 28.2).

Secondary endpoints

Complete remission (UC-DAI score = 0) at week 8 showed non-inferiority and was numerically but not significantly higher with OD compared with BD dosing (35.5% vs. 29.2%, $P = 0.37$; OC analysis). Significantly more patients in the OD group achieved an improvement in UC-DAI score at week 8 compared with the BD group (92% vs. 79%, respectively, $P = 0.01$, OC analysis). The OD regimen was non-inferior to the BD regimen in terms of clinical remission at both week 4 and week 8 when patients with missing data were considered to be in nonremission (Table 2). By only considering the 83 patients who were in clinical and endoscopic remission at week 8 (UC-DAI score ≤ 1) who continued the study to week 12, the OD regimen was proven to be non-inferior to the BD regimen for clinical remission at week 12 (UC-DAI abbreviated sub-score = 0). The rates of clinical remission at week 12 among patients who had an UC-DAI score of ≤ 1 at week 8 were 80.1% in the OD group and 73.2% in the BD group (95% CI: −11.5, 25.4; $P = 0.46$). Time to remission was significantly shorter in the OD dosing arm compared with BD dosing (26 days

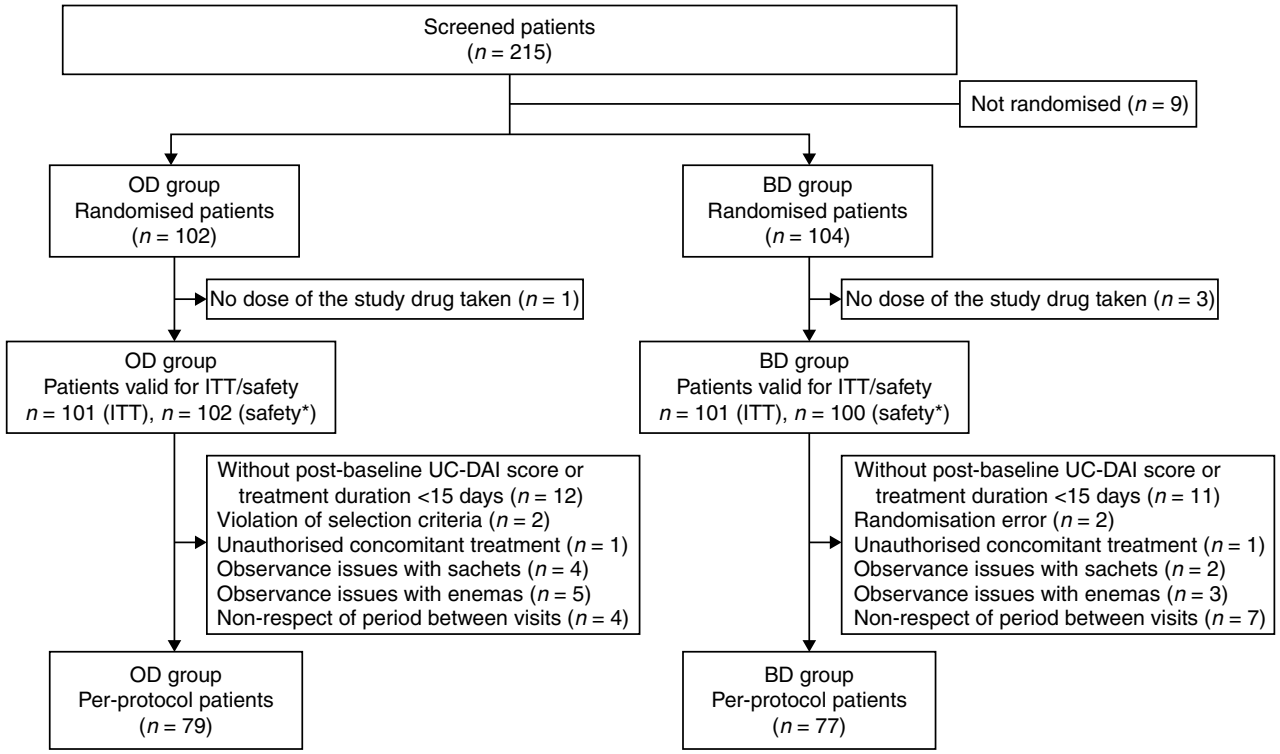

Figure 1 | CONSORT diagram describing the progress of patients throughout the course of the MOTUS study. BD, twice-daily; DAI, disease activity index; ITT, intent-to-treat; OD, once-daily; UC, ulcerative colitis.

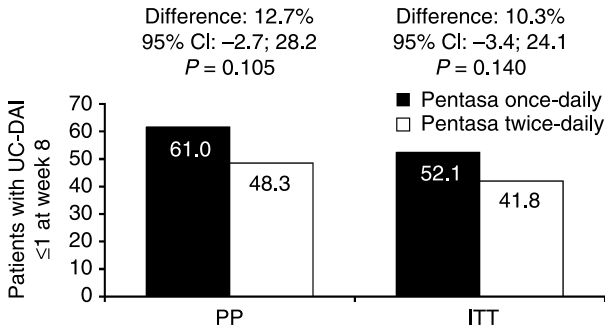

Figure 2 | Clinical and endoscopic remission rates at week 8. Percentage of patients achieving remission (UC-DAI ≤ 1) in the ITT and PP populations for OD vs. BD prolonged-released mesalazine treatment for mild-to-moderate UC. BD, twice-daily; CI, confidence interval; DAI, disease activity index; ITT, intent-to-treat; OD, once-daily; PP, per-protocol; UC, ulcerative colitis.

vs. 28 days, $P = 0.04$). Mucosal healing rates, assessed by UC-DAI endoscopic sub-score ≤ 1, were significantly higher with OD dosing (87.5% vs. 71.1% with BD dosing, $P = 0.007$; OC analysis; Figure 3); when assessed by UC-DAI endoscopic sub-score = 0, these rates were numerically but not statistically higher with OD dosing (47.6% vs. 36.8%, $P = 0.145$; Figure 3). Endoscopic remission (Rachmilewitz index <4) was also numerically but not statistically higher with OD dosing (70.2% vs. 61.1% with BD dosing, $P = 0.20$; Table 2).

Subgroup analysis

The primary endpoint of clinical and endoscopic remission at week 8 (UC-DAI score ≤ 1) and secondary endpoints of complete remission at week 8 (UC-DAI score = 0) and mucosal healing at week 8 (UC-DAI endoscopic sub-score ≤ 1) were evaluated in a subgroup analysis comparing patients with left-sided disease location with the total study population. Patients with left-sided or distal UC comprised 83% of the overall population (pancolitis or extensive UC comprised 17%); 81% of the OD arm and 85% of the BD arm had left-sided/distal UC (OD, $n = 83$; BD, $n = 88$). In patients with left-sided/distal UC, the primary endpoint of clinical and endoscopic remission rate was 52.9% with OD dosing and 41.5% with BD dosing (lower 95% CI limit −3.7%, $P = 0.139$). In a post hoc analysis, patients with left-sided/

Table 2 | Secondary endpoints analysis in the ITT population for OD vs. BD prolonged-release mesalazine treatment for active mild-to-moderate UC

	OD (n = 102)	BD (n = 104)	95% CI	P-value
Complete remission at week 8*, %	35.5	29.2	−7.4, 20.0	0.37
Improvement of UC-DAI at week 8*, %	92.0	79.0	2.5, 23.5	0.01
Clinical remission, %				
Week 4†	39.8	27.8	−0.9, 25.3	0.07
Week 8†	45.1	40.8	−9.2, 18.0	0.42
Median time to remission*, days (range)	26 (13–30)	28 (15–45)	_	0.04
Mucosal healing at week 8*, %				
UC-DAI sub-score ≤1	87.5	71.1	4.5, 28.2	0.007
UC-DAI sub-score = 0	47.6	36.8	−3.7, 25.2	0.145
Rachmilewitz endoscopic index <4*, %	70.2	61.1	−4.8, 23.0	0.20

BD, twice-daily; CI, confidence interval; DAI, disease activity index; ITT, intent-to-treat; OD, once-daily; UC, ulcerative colitis.

* Observed cases analysis.

† Missing data set as nonremission.

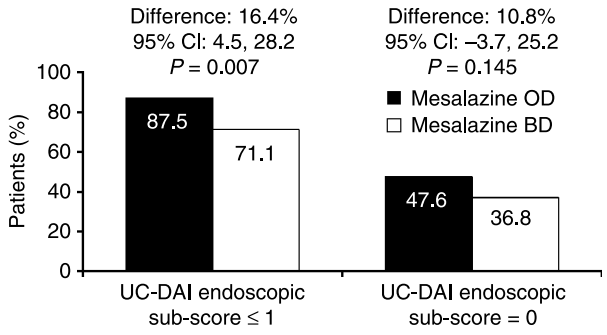

Figure 3 | Mucosal healing rates at week 8. Percentage of patients achieving mucosal healing (UC-DAI endoscopic sub-score = 1 or 0) in the ITT population (observed cases analysis) for OD vs. BD prolonged-released mesalazine treatment for mild-to-moderate UC. BD, twice-daily; CI, confidence interval; DAI, disease activity index; ITT, intent-to-treat; OD, once-daily; UC, ulcerative colitis.

distal UC complete remission rates were 28.0% with OD dosing vs. 24.4% with BD dosing (lower 95% CI limit −9.9%, P = 0.605) and mucosal healing (endoscopic sub-score of UC-DAI ≤1) rates were 86.6% with OD dosing vs. 68.2% with BD dosing (lower 95% CI limit −5%, P = 0.007).

Compliance

Acceptability and compliance were similar for both arms of the study. Acceptability was numerically but not statistically higher at week 8 in the OD arm compared with the BD arm [mean (s.d.): OD 73.2 (22.3)%, BD 66.3 (29.4)%; P = 0.10]. Compliance was high with median compliance rates of 100% observed for oral mesalazine and mesalazine enema in both treatment arms. Mean (s.d.) compliance with oral mesalazine was 104 (±23.7%) in the OD group and 108 (±65.4%) in the BD group (P = 0.448), indicating that some patients returned less study medication than was expected from the protocol.

Safety

A total of 202 patients (102 in the OD group, 100 in the BD group) received at least one dose of prolonged-release mesalazine and were designated as the safety population. During the course of the study, 35 patients (34.3%) in the OD group and 38 patients (38%) in the BD group experienced at least one AE (not significant). A total of 67 patients (33.2%) experienced at least one treatment-emergent AE: 33 (32.4%) and 34 (34.0%) patients in the OD and BD groups respectively. The most frequent treatment-emergent AEs are given in Table 3. Among these 67 patients, 10 patients (9.8%) in the OD group and 10 patients (10.0%) in the BD group

Table 3 | TEAEs seen with OD vs. BD prolonged-release mesalazine treatment of active mild-to-moderate UC

	OD (n = 102), n (%)	BD (n = 100), n (%)	Total (n = 202), n (%)
Any TEAE	33 (32.4)	34 (34.0)	67 (33.2)
TEAE experienced by >2% of patients			
Abdominal pain	3 (2.9)	4 (4.0)	7 (3.5)
Nausea	5 (4.9)	2 (2.0)	7 (3.5)
Headache	3 (2.9)	3 (3.0)	6 (3.0)
Worsening UC	2 (2.0)	3 (3.0)	5 (2.5)
Pyrexia	3 (2.9)	2 (2.0)	5 (2.5)
Proctalgia	4 (3.9)	0 (0.0)	4 (2.0)
Arthralgia	1 (1.0)	3 (3.0)	4 (2.0)
Asthenia	1 (1.0)	3 (3.0)	4 (2.0)

BD, twice-daily; OD, once-daily; TEAE, treatment-emergent adverse event; UC, ulcerative colitis.

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presented with at least one treatment-related, treatment-emergent AE. All treatment-emergent AEs were mild-to-moderate in intensity. Serious AEs were experienced by five patients (4.9%) in the OD group and three patients (3.0%) in the BD group. Two patients experienced serious AEs that were considered related to treatment; one patient in the BD group with hepatitis and one patient in the OD group with polyuria, chromaturia and a mild increase in blood creatinine levels. Both patients with serious AEs discontinued the trial and recovered without treatment.

There were no notable differences in terms of changes in laboratory results or vital signs between the two study groups. Creatinine plasma levels, platelets, white blood cell count, red blood cell count, haemoglobin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase and gamma-glutamyltranspeptidase (other than the two cases previously described) were all tested and found to be within normal range for both treatment groups.

DISCUSSION

This study showed that an OD (morning) regimen of 4 g prolonged-release mesalazine is non-inferior to a BD divided dose regimen. Non-inferiority was shown for the primary endpoint of clinical and endoscopic remission at week 8 as the 95% CI was between −15% and 0% (−3.4, 24.1), despite the required sample size for the protocol not being achieved. Serious difficulties in recruitment, despite extension of the study by 6 months and inclusion of additional centres, resulted in incomplete patient numbers, and therefore premature ending of the study and analysis of the patients recruited to date. These recruitment difficulties may have been due to the high number of competing clinical trials/programmes in active UC across Western Europe. The difference in the primary endpoint between the two dosing regimens was greater than 10% and favoured the OD regimen. A post hoc calculation of power based on the ITT analysis of the primary endpoint gave a power of 94% (standard proportion 42%, test proportion 52% and sample size $n = 101$). Using results from the PP analysis gave the same power, showing that non-inferiority was demonstrated in this study.

The 8-week remission rates seen in our trial (52.1% with OD and 41.8% with BD dosing in the ITT population) are lower than seen in the PINCE study (64%),[12] which compared combined oral (BD) and enema treatment of prolonged-release mesalazine with the oral formulation alone (BD) in patients with extensive mild-to-moderate UC. However, the studies handled missing data differently, with PINCE marking patients with no available endoscopy data as in remission; whereas in the MOTUS study, such patients would have been classed as being in nonremission. Also, patients had higher baseline UC-DAI scores in the MOTUS study (UC-DAI score = 6) compared with PINCE (UC-DAI score = 4.7) indicating more moderate than mild patients in MOTUS, which could result in lower remission rates. In addition, patient populations in the two studies had different disease extension, with PINCE requiring extensive disease extension beyond the splenic flexure, whereas 83% of the MOTUS population had left-sided or distal extension.

The secondary endpoints, which included clinical remission at week 4 and complete remission at week 8, also showed non-inferiority for the OD regimen compared with the BD regimen. Improvement in UC-DAI score was significantly higher with OD vs. BD dosing ($P = 0.01$) and time to remission was significantly shorter in the OD arm compared with the BD arm ($P = 0.04$). For the secondary endpoint of mucosal healing (UC-DAI endoscopic sub-score ≤ 1), the OD treatment was significantly better than the BD regimen ($P < 0.01$). Mucosal healing has been correlated with long-term disease remission rates, a reduced need for colectomy, reduced risk of colorectal cancer and improved patient quality of life.[15, 16] Although a number of studies have used this as an important endpoint, a standard definition of mucosal healing is needed for inter-trial comparisons before mucosal healing can be used to guide therapy choices.[17] Demonstrating efficacy for both clinical and endoscopic endpoints in MOTUS shows promise for this OD regimen in aiding long-term remission beyond that achieved with treatment showing only efficacy in clinical remission.

The endpoints measured in the subgroup analysis for patients with left-sided/distal UC were comparable to those seen in the overall population. These results show that prolonged-release mesalazine has similar efficacy in patients with left-sided UC and those in the overall MOTUS trial population with regard to inducing clinical and endoscopic remission. Similar results between the left-sided population and the overall population were also seen in the PODIUM trial investigating prolonged-release mesalazine for the maintenance of remission.[18]

Our findings are in line with other studies that have investigated single- vs. multi-dose regimens of the same formulation of mesalazine given at similar total daily dose in active UC. Kamm *et al.* demonstrated clinical and endoscopic remission rates (defined as a modified UC-DAI score ≤ 1) at week 8 of 40.5% with MMX mesalazine 2.4 g/day OD (ITT population),[8] whereas Lichtenstein *et al.* showed remission rates of 34.1% with

MMX mesalazine 2.4 g/day BD.[9] The clinical and endoscopic remission rate at week 8 seen in MOTUS is 8–12% higher than that achieved with MMX mesalazine. This may be explained by: (i) the higher remission rate with combination treatment (oral and enema) compared with oral treatment alone, as demonstrated in the PINCE study,[12] and (ii) the lower daily dose of MMX mesalazine (2.4 g vs. 4.0 g), although the remission rates shown with MMX mesalazine 4.8 g/day only tested OD in the MMX mesalazine studies[8, 9] were roughly similar to those obtained with MMX mesalazine 2.4 g/day (35.1% vs. 37.2% with 4.8 g/day vs. 2.4 g/day respectively) in the combined analysis performed by Sandborn *et al.*[19] Lastly, the modified UC-DAI used in the MMX mesalazine studies moved mucosal friability from score 1 to 2, which could reduce the remission rates found in studies with MMX mesalazine. Kruis *et al.* showed that OD dosing of mesalazine granules (3 g/day) was non-inferior to three-times daily (TID) dosing for inducing clinical remission, defined as a clinical activity index score of ≤ 4.[10] In the OD arm, 79.1% of patients achieved clinical remission and 75.7% of those in the TID arm achieved clinical remission at 8 weeks. Kruis *et al.* also performed a post hoc analysis using the modified UC-DAI ≤ 1 scoring system. These results showed a OD remission rate of 37% and a TID remission rate of 39% (ITT population).[10]

In all previous studies cited above, remission rates tended to be higher with single- compared to multi-dose regimens (except for the post hoc analysis in the Kruis *et al.*'s study). Moreover, in our study, the OD regimen was superior to the BD regimen for some endpoints. As suggested by Kruis *et al.*, OD dosing could lead to a higher peak luminal concentration and higher mucosal concentration of mesalazine compared with divided dosing given at a similar total daily dose.[10] The improved rate of mucosal healing achieved with the OD regimen would be consistent with this hypothesis. Measurement of mucosal concentrations of mesalazine after OD or BD regimen could help to verify this hypothesis. The superiority of OD dosing over BD dosing cannot be attributed to improved compliance and/or acceptability in the OD group, as these endpoints were similar in the two treatment arms. A difference in compliance between the two dosing regimens was not expected as patients were: (i) either newly diagnosed and/or relapsing and therefore likely to be seeking effective treatment, (ii) in a tightly controlled clinical trial environment undergoing regular assessments with a physician, and (iii) likely to be highly motivated given their willingness to participate in a clinical trial.

OD administration of prolonged-release mesalazine was well tolerated, with no new safety concerns arising from this study. The majority of AEs relating to the study were mild-to-moderate in intensity and acceptable to patients. The percentage of patients experiencing at least one AE with the 4 g OD dose (34.3%) was comparable to that seen in a study where patients were given a similar mesalazine dose of 3 g OD (28.8%)[10] or a dose of 4.8 g MMX mesalazine (40.4%).[9] The rate of the most common treatment-emergent AE (gastrointestinal disorders) in MOTUS (7.8% in OD group) was comparable to that seen in both Kamm *et al.* (8.2%)[8] and in Lichtenstein *et al.* (5.3%) for 4.8 g mesalazine MMX OD dosing.[9] Only two serious AEs were deemed related to treatment. The case of hepatitis and the case of increased creatinine levels, polyuria and chromaturia were mild in intensity. These two events are well-characterised mesalazine-associated events, which are likely due to hypersensitivity and not related to dose.[20–22] The safety data seen in MOTUS confirm that 4 g of mesalazine taken in a single dose raises no new safety concerns compared with multi-dosing regimens.

During acute disease flares, UC has an impact on patients' quality of life and the use of complicated multi-dosing regimens further disrupts normal daily life. It is important that treatment regimens are as convenient as possible without compromising efficacy. The MOTUS study has shown that OD prolonged-release mesalazine (4 g) is as effective as BD divided dosing 2×2 g in achieving remission in patients with mild-to-moderate active UC. This positive finding was also confirmed by secondary endpoint analysis. It was also shown that OD dosing may offer benefits as well as being more convenient for patients as clinical and endoscopic improvement was higher, time to remission was shorter and mucosal healing was increased compared with BD dosing. In conclusion, the OD oral dose of prolonged-release mesalazine is an effective and easy to use treatment for patients with mild-to-moderate active UC.

AUTHORSHIP

Guarantor of the article: Flourié.

Author contributions: Flourié, Hagège, Tucat and Aoucheta designed the study. Flourié, Hagège, Tucat, Maetz, Hébuterne, Kuyvenhoven, Tan, Pierik, Masclee, Dewit and Probert contributed to the acquisition/collection of data. Flourié, Hagège, Tucat, Maetz, Hébuterne, Kuyvenhoven, Tan, Pierik, Masclee, Dewit, Probert, Aoucheta performed the analysis of data. Flourié, Hagège,

Tucat, Maetz, Hébuterne, Kuyvenhoven, Tan, Pierik, Masclee, Dewit, Probert and Aoucheta performed the interpretation of data. All authors approved the final version of this manuscript, including the authorship list.

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