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Mesalamine Once Daily Is More Effective Than Twice Daily in Patients With Quiescent Ulcerative Colitis

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See related article, Migaleddu V et al, on page 43 in *Gastroenterology*.

BACKGROUND & AIMS: Oral mesalamine (5-aminosalicylate) is the current standard of care for mild-to-moderate ulcerative colitis. We investigated the efficacy and safety of once daily administration of prolonged-release mesalamine granules in maintenance of remission in patients with quiescent ulcerative colitis, compared with the well established twice daily dosing regimen. **METHODS:** In this multicenter, randomized, single blind, noninferiority trial, 362 patients with quiescent ulcerative colitis were randomly assigned (1:1) to groups that were given oral mesalamine 2 g, once daily, or 1 g, twice daily, for 12 months. The primary objective was to compare remission rates at 1 year, based on the ulcerative colitis disease activity index score, using Kaplan–Meier methodology. **RESULTS:** At 1 year, 70.9% of the group given 2 g mesalamine once daily remained in remission vs 58.9% of the group given 1 g mesalamine twice daily; this difference was statistically significant ($P = .024$), indicating the increased efficacy of once daily, compared with twice daily, dosing. Self-reported adherence to therapy, measured by visual analog scale score after 4, 8, and 12 months, was significantly greater in the group given 2 g mesalamine once daily, compared with twice daily, at all but 1 study visit ($P < .05$). Compliance measured by medication taken was not significantly different between the groups. The difference between the 2 groups in overall incidence of adverse events was not statistically significant ($P = .23$). **CONCLUSIONS: Patients with ulcerative colitis given prolonged-release oral mesalamine 2 g once daily had better remission rates, acceptability, and self-reported adherence to therapy compared with patients given oral mesalamine 1 g twice daily.**

Ulcerative colitis (UC) is a chronic inflammatory disorder of the colon, affecting 1 in 1000 people in the Western world.[1] It is characterized by periods of quiescence punctuated by intermittent episodes of acute exacerbation, with a relapse risk of up to 50% per year.[2] Oral mesalamine (5-aminosalicylate [5-ASA]) is an established treatment for UC and the current standard of care. It is effective and well tolerated at doses of up to 4.8 g/day in active UC[3–7] and >800 mg/day for maintenance of remission,[8–12] although a clear dose-response effect has yet to be established. Several different oral formulations of mesalamine have been developed, allowing flexibility of dose and dosing frequency.[13]

Pharmacokinetic studies in healthy volunteers suggest that once daily dosing may be an effective option in patients with UC. Hussain et al[14] showed that serum, urinary, fecal, and rectal tissue concentrations were similar for once and three times daily mesalamine dosing regimens. Also, in a recent study, 4 g oral ethylcellulose-coated mesalamine given once daily was bioequivalent to a twice daily regimen after single or repeated administration.[15] While several randomized controlled trials have investigated once versus multiple daily dosing regimens with Multi Matrix System mesalamine (Shire Pharmaceuticals, Wayne, PA)[16,17] or Eudragit (Röhm & Haas, Darmstadt, Germany) coated mesalamine[18] for the induction of remission in active UC, only 2 studies have investigated once daily mesalamine versus conventional dosing in maintaining quiescent UC. The first was a small 6-month pilot study, which showed similar rates of clinical relapse in the once daily and conventional dosing groups.[19] The second was a randomized, open label, 12-month study to establish the safety profile of once versus twice daily Multi Matrix System mesalamine.[20] As a secondary endpoint, the study established that both regimens were equally effective at maintaining patients in remission (64.4% vs 68.5% of patients at 1 year; $P = .351$).

While these data are encouraging, there remains a need to demonstrate in a robust clinical trial, with efficacy as a primary endpoint, that once daily mesalamine is at least as effective as established dosing regimens in quiescent UC, and to investigate new treatment strategies to improve adherence. Most patients with UC require long term maintenance treatment, but adherence rates in quiescent UC may be as low as 40% outside of the clinical trial setting.[21] Multiple daily dosing is an independent predictor of partial noncompliance with medication in inflammatory bowel disease,[22] and noncompliance significantly increases the risk of clinical relapse in quiescent UC ($P < .001$).[23]

Abbreviations used in this paper: 5-ASA, 5-aminosalicylic acid (mesalamine); BID, twice daily; CI, confidence interval; ITT, intent-to-treat; OD, once daily; PP, per protocol; UC, ulcerative colitis; UC-DAI, ulcerative colitis disease activity index; VAS, visual analog scale.

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The primary objective of this noninferiority study (PODIUM-FE99907; ClinicalTrials.gov Identifier: NCT00209300) was to show that once daily dosing of prolonged-release mesalamine 2 g sachets (Pentasa®, Ferring Pharmaceuticals, Saint-Prex, Switzerland) was noninferior to conventional twice daily dosing of prolonged-release mesalamine (Pentasa®) 1 g sachets for maintenance of remission in patients with mild to moderate UC. Compliance was evaluated as a secondary endpoint.

Materials and Methods

Participants

Male and female patients aged ≥18 years with an established diagnosis of UC, with disease >15 cm from the anal verge, and in clinical remission (based on a UC disease activity index [UC-DAI] score[24] <2 at enrolment) were eligible for inclusion. Other inclusion criteria were clinical relapse (requiring adjustment of maintenance therapy) within 12 months prior to study entry, and maintenance treatment with oral mesalamine (≤2.5 g/day), sulfasalazine (≤3.0 g/day) or olsalazine (≤1.5 g/day) at randomization. Patients who were not using these drugs at randomization, but who had received oral mesalamine, sulfasalazine or olsalazine in the 12 months prior to the study, were also eligible for inclusion.

Patients were excluded if they had evidence of other forms of inflammatory bowel disease, idiopathic proctitis, or infectious disease, had abnormal hepatic or renal function, or a history of alcohol or drug abuse. Other exclusion criteria were the use of the following drugs within 1 month of study entry: oral mesalamine, sulfasalazine, or olsalazine at doses >2.5 g/day, >3.0 g/day, or >1.5 g day, respectively; rectal mesalamine (>3 g/week) or sulfasalazine (>3 g/week); and orally or rectally administered corticosteroids; or use of immunosuppressants within the previous 3 months. Pregnant and lactating women and patients with an allergy to acetylsalicylic acid and other salicylate derivates were also excluded.

During the study, patients were prohibited from taking concurrent medications for UC, including >2 consecutive days' medication for symptomatic relief of possible relapse, use of nonsteroidal anti-inflammatory drugs for >2 days/week for symptoms of increased disease activity, antibiotics for treatment of relapse, and any medication proven to be efficacious for maintenance of remission.

The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and local Institutional Review Boards or Independent Ethics Committees. All patients gave written informed consent.

Study Design

PODIUM (Pentasa® Once Daily In Ulcerative colitis for Maintenance of remission) was a European, multicenter, randomized, phase III, single blind, parallel group, controlled, noninferiority trial, to compare the efficacy and safety of 2 dosing intervals (once daily [OD] versus twice daily [BID]) of oral mesalamine (2 g/day) for the maintenance treatment of UC.

After a 7-day screening period, eligible patients were randomized (1:1) on day 0 to receive oral ethylcellulose-coated mesalamine (Pentasa®; 2 g/day) for 12 months, according to 2 treatment schedules: 2 g OD or 1 g BID (reference treatment), supplied as either 2 g or 1 g sachets. Patients were randomized centrally using an interactive voice response system, and in randomly permuted blocks of variable size stratified for each center. As this study evaluated the impact of dosing frequency on compliance, it was designed as a single blind study, where investigators were blinded to study medication and patients urged not to reveal their treatment schedule. Medication was supplied to patients in identical neutral boxes; unused study medication was returned in a sealed box, and drug usage was assessed by qualified personnel, other than the investigator.

Patients visited the clinic on 5 occasions: screening visit at week –1; baseline visit at week 0 (randomization); and visits at 4, 8, and 12 months (study end) ± 2 weeks, or within 1 week of relapse or withdrawal. Hematology, clinical laboratory (renal and liver function tests), and sigmoidoscopy (mucosal appearance) assessments were undertaken at the screening and end of study visits. Physical examination and vital signs were evaluated at baseline and study end. The following assessments were made at baseline and months 4, 8, and 12: activity of illness using UC-DAI score (abbreviated UC-DAI without endoscopic assessment at months 4 and 8), concomitant medication use, and tobacco consumption. In addition, information on number of stools and rectal bleeding for the 3 days prior to each visit were collected from patients' diaries. At months 4, 8, and 12, global acceptability of treatment and compliance assessments were made. Additional laboratory safety evaluations could be undertaken during the study, and adverse events were elicited at each clinic visit using standard nonleading questions.

Objectives

The primary objective of the study was to compare the 1-year remission rates in the 2 mesalamine treatment groups and show that the once daily dose is noninferior to the twice daily regimen. It was also hypothesized that the lower dosing frequency with 2 g mesalamine OD might lead to improved compliance, which is a prerequisite for remaining in remission. In the primary analysis, remission rates were measured using the UC-DAI score.[24,25] Remission was defined as a UC-DAI score <2. For the end of study analysis, patients with a UC-DAI score of 2, without adjustment of treatment for UC, were regarded as being in remission, while those with treatment adjustment were considered as having relapsed. UC-DAI scores of 3–8 were classified as mild to moderate UC, while scores >8 were considered as severe relapse.

Secondary endpoints included comparison of time to relapse between treatment groups, and comparison of UC-DAI total and subscores to measure severity of relapse. Sigmoidoscopy assessments at baseline and at study end (or upon withdrawal/discontinuation) using the UC-DAI 3-point scoring system were also evaluated. Compliance with medication was assessed by recording the number of mesalamine sachets dispensed and returned, as well as a validated questionnaire for self-reported adherence to treatment[26] and a 100 mm visual analog scale (VAS) score delimited from 0 (not adherent) to 100 (completely adherent).[22] Patients' global acceptability of treatment was assessed using a 100 mm VAS delimited from 0 (frequency of drug intake per day not acceptable) to 100 (frequency of drug intake per day acceptable). The safety and tolerability of the 2 dosing regimens were also compared.

Sample Size

The study was powered as a noninferiority study and sample size calculations were based on an expected 1-year remission rate (primary endpoint) of 60% for 1 g mesalamine BID. A 1-year remission rate of 65% was estimated for the OD group—this modest improvement in remission rate was based on an expected improvement in compliance outweighing any biological disadvantage of a reduction in the number of daily doses. Based on clinical judgment, once daily dosing with mesalamine was gauged to be not worth more than a 10% loss in remission rate. Taking these estimations into consideration, the noninferiority limit was specified as 10%. To obtain 80% statistical power with a 1-sided α equal to .025, and a noninferiority limit of 10%, approximately 163 patients were needed in each study arm. To account for a possible 10% dropout rate, the planned sample size was 360 patients (180 in each treatment group).

Statistical Methods

The intent-to-treat (ITT) population was defined as all randomized patients who received treatment and had at least 1 post-baseline efficacy assessment. Two per protocol (PP) populations were evaluated: PP1 was defined as the ITT population, with patients who dropped out of the study censored at the time of dropout, and PP2 was defined as the ITT population, excluding dropouts. The safety population included all randomized patients.

The primary analysis was the comparison of 1-year remission rates, calculated using Kaplan–Meier survival curves for relapse. To demonstrate noninferiority, the 2-sided 95% confidence interval (CI) for the difference between groups had to exclude a more than 10% difference to the disadvantage of 2 g OD. The Z-test was used to test the null hypothesis of no difference between the 1-year remission rates.

For the prespecified secondary efficacy analyses, all statistical tests were stratified by study center. Differences between treatments were considered statistically significant if $P < .05$. Time to relapse was analyzed using Kaplan–Meier survival curves using the log-rank test to assess differences between groups. The estimate of treatment effect was expressed as a hazard ratio with 95% CI. Severity of relapse in the PP1 population was estimated by the distribution of total and subscores at each visit and mean (SD) total UC-DAI scores. Treatments were compared using the Wilcoxon rank sum test. Changes in the percentage of medication used in the periods 0–4 months, 5–8 months, and end of study, presented as a weighted mean (by length of period) for the duration the patient remained in the trial, were analyzed across the 2 treatment groups using the Wilcoxon rank sum test. Compliance measured by questionnaire and VAS, and acceptability of treatment, were also analyzed using the Wilcoxon rank sum test. To test for any effect of compliance on treatment outcome, a Cox proportional hazards regression model was undertaken on the UC-DAI remission rate, with compliance with medication per 4-month treatment period used as a covariate. Post-hoc survival analyses were also undertaken on the UC-DAI remission rates and time to relapse using duration of disease as a covariate, and also by stratifying patients according to type of disease (left-sided UC or pancolitis), and age/gender (<35 years vs ≥35 years).

The safety population was used for safety assessments, and group summary statistics were calculated. Adverse events were compared between treatment groups using Fisher's exact test.

Results

Patient Demographics

The study was conducted between May 2005 and May 2007 with patients screened at 68 centers in 8 European countries (Belgium, Czech Republic, Denmark, Finland, Germany, The Netherlands, Norway, and Sweden). A total of 362 patients were randomized to prolonged-release mesalamine 2 g OD (n = 175) or prolonged-release mesalamine 1 g BID (n = 187), with 315 patients completing the study (2 g OD, n = 153; 1 g BID, n = 162). Six patients in the OD group and 3 in the BID group were excluded from the ITT population because of major entry criteria violation. Figure 1 shows the patient flow and reasons for discontinuation.

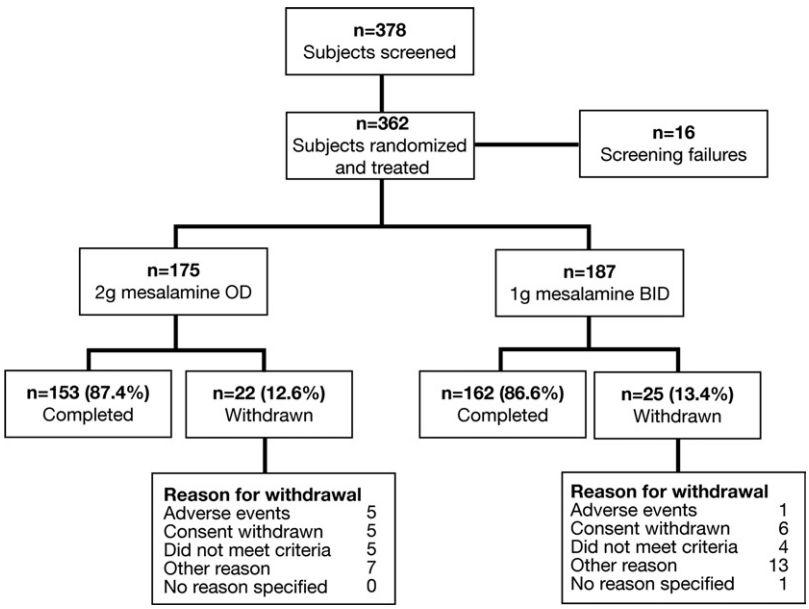

Figure 1. Schematic representation of patient flow and reasons for discontinuation.

Table 1. Baseline Characteristics and Demographics of Randomized Patients

	2 g Mesalamine OD N = 175	1 g Mesalamine BID N = 187	Total N = 362
Gender, n (%)			
Male	95 (54.3)	96 (51.3)	191 (52.8)
Female	80 (45.7)	91 (48.7)	171 (47.2)
Age, *y*			
Mean (SD)	48.7 (15.0)	47.2 (14.1)	48.0 (14.6)
Range	19–80	18–82	18–82
Weight, *kg*			
Mean (SD)	76.7 (14.8)	76.4 (15.1)	76.5 (14.9)
BMI, kg/m^2			
Mean (SD)	25.5 (3.8)	25.4 (4.0)	25.5 (3.9)
Smoking status, n (%)			
Currently smoking	21 (12.0)	21 (11.2)	42 (11.6)
Smoked in past	69 (39.4)	87 (46.5)	156 (43.1)
Never smoked	85 (48.6)	79 (42.2)	164 (45.3)
Type of disease, n (%)			
Pancolitis	44 (25.1)	59 (31.6)	103 (28.5)
Left-sided colitis	131 (74.9)	128 (68.4)	259 (71.5)
Stool frequency, n (%)			
Normal	170 (97.1)	183 (97.9)	353 (97.5)
1–2.4 times above normal/day	5 (2.9)	4 (2.1)	9 (2.5)
Rectal bleeding, n (%)			
None	173 (98.9)	183 (97.9)	356 (98.3)
Traces of blood	2 (1.1)	4 (2.1)	6 (1.7)
Mucosal appearance, n (%)			
Normal	95 (54.3)	109[a] (58.6)	204 (56.5)
Erythema	79 (45.1)	76 (40.9)	155 (42.9)
Friability	1 (0.6)	1 (0.5)	2 (0.6)
Global assessment, n (%)			
No active disease	171 (97.7)	183[a] (98.4)	354 (98.1)
Mild disease	4 (2.3)	3 (1.6)	7 (1.9)
UC-DAI total score, mean (SD)	0.53 (0.52)	0.48 (0.52)	0.50 (0.52)
Range	0–2	0–2	0–2
Patient in remission, n (%)	173 (98.9)	184[a] (98.9)	357 (98.9)

BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
[a]Data missing for 1 patient.

Patient demographic and baseline characteristics were not significantly different between treatment groups (Table 1) and were generally representative of those typically seen in UC.

Efficacy

The study met its primary efficacy endpoint, with 2 g mesalamine OD being not only noninferior, but statistically significantly superior, to 1 g mesalamine BID in maintaining patients in remission. Kaplan–Meier estimated UC-DAI remission rates at 1 year after randomization (Figure 2) showed a statistically significant difference of 11.9% (95% CI, 1.4–22.5) in favor of OD treatment, with 70.9% remaining in remission compared with 58.9% of the BID group ($P = .024$; ITT analysis). Kaplan–Meier estimated remission rates were also statistically significantly superior for the OD group in the PP1 and PP2 populations ($P = .021$ and $P = .009$, respectively). At end of study, UC-DAI remission rates were 73.8% (121/164; 95% CI, 67.0–80.6) in the OD group and 63.6% (110/173; 95% CI, 56.4–70.8) in the BID group (ITT analysis).

Analysis of the secondary efficacy endpoints supported the primary efficacy results. Time to relapse tended to be longer with OD treatment compared with the BID group (median 202.0 days vs 148.0 days; $P = .08$, log rank test; ITT analysis). The UC-DAI subscores "stool frequency," "rectal bleeding," and "physician's global assessment" (Table 2) were more frequently categorized as "normal" during OD treatment (81.5%, 79.6%, and 72.3%, respectively) than with BID dosing (67.7%, 70.7%, and 62.5%, respectively). In addition, the mean UC-DAI total score at end of study was lower in the OD treatment group (1.74) compared with the BID group (2.33), although the difference was not statistically significant ($P = .061$). Endoscopic evaluation of mucosal appearance was measured in the PP1 population (discontinuers excluded) and revealed a lower mean mucosa score after treatment with 2 g mesalamine OD (0.70) than for 1 g mesalamine BID (0.75), though the difference was not statistically significant.

Results of the post-hoc analyses showed no significant effect of patient age and gender, duration, or type of disease (left-sided UC or pancolitis) on UC-DAI remission rates or time to relapse (data not shown).

Compliance

The primary measure of compliance was the percentage of mesalamine sachets used. Although this was higher for the OD vs the BID treatment group at each visit (Table 3), the differences were not statistically significant. However, compli-

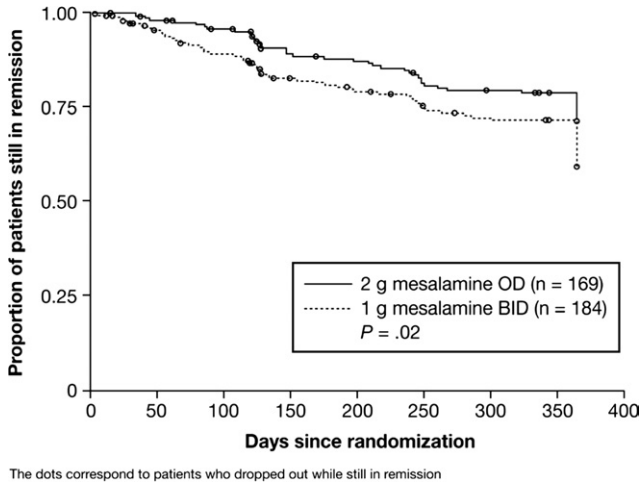

Figure 2. Kaplan–Meier estimated UC-DAI remission rates, where remission is defined as a UC-DAI total score <2.

ance measured by the VAS score (Table 3) was better for the OD group than for the BID group, with the difference being significant at all time points except the end of study visit.

Compliance was also assessed by a validated questionnaire. In the BID group, 25%–44% of patients indicated that they sometimes forgot to take their medication, compared with 21%–26% in the OD group. Furthermore, in the BID group, 15%–21% of patients responded that they had been careless about medication compared with 12%–15% in the OD group. No clear differences were found for the questions relating to sometimes stopping medication if the patient felt better/worse.

VAS scores showed significantly improved acceptability of treatment for the OD group compared with the BID group at all visits (Table 4), with the difference being most pronounced at end of study.

Table 2. UC-DAI Total Score and Subscale Scores at End of Study (PP1 Population)

	2 g Mesalamine OD	1 g Mesalamine BID
	n/N[a] (%)	n/N[a] (%)
Total score		
Remission (UC-DAI <2)	106/146 (72.6)	95/157 (60.5)
Mild relapse (2–3)	7/146 (4.8)	9/157 (5.7)
Mild-to-moderate UC (3–8)	27/146 (18.5)	46/157 (29.3)
Severe relapse (>8)	6/146 (4.1)	7/157 (4.5)
Stool frequency		
Normal	119/146 (81.5)	107/158 (67.7)
1–2.4 times above normal/day	7/146 (4.8)	22/158 (13.9)
2.5–4 times above normal/day	12/146 (8.2)	12/158 (7.6)
>4 times above normal/day	8/146 (5.5)	17/158 (10.8)
Rectal bleeding		
None	117/147 (79.6)	111/157 (70.7)
Traces of blood	14/147 (9.5)	18/157 (11.5)
Frank blood	11/147 (7.5)	26/157 (16.6)
Mainly blood	5/147 (3.4)	2/157 (1.3)
Physician's global assessment		
No active disease	107/148 (72.3)	100/160 (62.5)
Mild disease	25/148 (16.9)	33/160 (20.6)
Moderate disease	14/148 (9.5)	25/160 (15.6)
Severe disease	2/148 (1.4)	2/160 (1.3)

PP1, per protocol group 1.
[a]N included number of patients with end of study (12 month) evaluations, and therefore excluded discontinuers.

Table 3. Compliance With Treatment According to Use of Mesalamine Sachets and VAS Score

	2 g Mesalamine OD		1 g Mesalamine BID		
	Mean (%)	SD	Mean (%)	SD	*P* value[a]
Sachets used					
ITT and PP1 samples					
Visit 2	78.8	21.1	74.6	23.3	.071
Visit 3	80.3	15.5	75.9	21.0	.053
End of study	79.1	16.8	79.8	19.3	.074
PP2 sample					
Visit 2	82.6	13.0	77.8	19.3	.033
Visit 3	80.5	14.3	77.1	19.3	.155
End of study	81.1	13.6	79.3	19.7	.080
VAS score (*mm*)					
ITT and PP1 samples					
Visit 2	95.6	10.4	94.0	8.8	.012
Visit 3	96.5	7.1	93.1	12.2	.002
End of study	94.5	13.7	93.2	13.0	.154
PP2 sample					
Visit 2	95.8	10.1	93.8	9.0	.006
Visit 3	96.7	7.0	92.9	12.5	.001
End of study	95.6	11.0	93.8	10.8	.033

PP1, per protocol group 1; PP2, per protocol group 2.
[a]Wilcoxon test stratified by country.

Impact of Compliance on Efficacy

When compliance per 4-month treatment period was used as a covariate, the treatment effect for OD vs BID was not significant ($P = .377$), while compliance was statistically significant ($P < .0001$).

Table 4. Acceptability of Treatment According to VAS Score

	2 g Mesalamine OD N = 169		1 g Mesalamine BID N = 184		
	Mean	SD	Mean	SD	*P* value[a]
ITT and PP1 samples					
Visit 2	95.8	9.7	83.8	25.7	.003
Visit 3	97.2	7.0	88.5	21.6	.049
End of study	96.3	10.0	85.6	24.4	.0001
PP2 sample					
Visit 2	96.2	8.8	83.8	25.5	.004
Visit 3	97.3	7.1	88.1	22.1	.059
End of study	96.2	10.3	87.3	23.2	.002

PP1, per protocol group 1; PP2, per protocol group 2.
[a]Wilcoxon test stratified by country.

Table 5. Treatment-Emergent Adverse Events Reported by at Least 2.0% of Patients in Any Treatment Group

	2 g Mesalamine OD N = 175	1 g Mesalamine BID N = 187
	N (%)	N (%)
Gastrointestinal disorder	35 (20.0)	24 (12.8)
Abdominal pain	6 (3.4)	5 (2.7)
Abdominal pain upper	4 (2.3)	3 (1.6)
Diarrhea	5 (2.9)	4 (2.1)
Flatulence	3 (1.7)	4 (2.1)
General disorders and administration site conditions	7 (4.0)	5 (2.7)
Infections and infestations	30 (17.1)	25 (13.4)
Bronchitis	2 (1.1)	5 (2.7)
Gastroenteritis	4 (2.3)	2 (1.1)
Nasopharyngitis	10 (5.7)	6 (3.2)
Sinusitis	6 (3.4)	2 (1.1)
Musculoskeletal/connective tissue disorders	11 (6.3)	6 (3.2)
Back pain	1 (0.6)	4 (2.1)
Nervous system disorders	5 (2.9)	6 (3.2)
Skin/subcutaneous tissue disorders	8 (4.6)	2 (1.1)

Safety

Overall, 42.9% of patients in the 2 g mesalamine OD group and 36.4% in the 1 g mesalamine BID group reported 1 or more adverse events. The overall incidence of adverse events was not significantly different between treatment groups ($P = .24$), and there was no difference in the types of adverse events (Table 5). The most frequently reported treatment-emergent adverse events were gastrointestinal disorders and infections/infestations. The majority of events were mild or moderate in intensity, and considered unrelated or unlikely related to study medication, with only 14 events being deemed possibly or probably related to treatment.

Six patients in the OD group and 4 in the BID group experienced serious adverse events, all of which were unrelated or unlikely related to study medication. In the OD group these were metastatic prostate cancer, myocardial ischemia, pyrexia, postoperative wound infection, squamous cell carcinoma, coronary artery disease, gastrointestinal ulcer hemorrhage, and cerebral hemorrhage resulting in patient death. Serious adverse events in the BID group were meningioma, migraine with aura, spondylolisthesis, chest pain, convulsion, and hypokalemia.

Discussion

This is the first long term (12-month) efficacy study designed to evaluate whether prolonged-release once daily mesalamine (2 g OD) can maintain remission in patients with quiescent UC. In this noninferiority study, mesalamine 2 g OD was not only noninferior to 1 g BID, but was actually superior in maintaining remission, with an 11.9% difference between groups at 12 months, which was an unexpected finding. The superiority of mesalamine 2 g OD was also supported by the secondary endpoints of the study, with a longer median time in remission (time to relapse), and improved UC-DAI subscores and mucosal appearance. The efficacy findings were consistent across the ITT and per protocol populations, indicating that patient withdrawals did not influence the study outcome.

Only 1 other published long term study has compared once daily versus twice daily mesalamine in the maintenance of remission in UC.[20] Although this was primarily a safety study, the secondary endpoint supported our hypothesis that once daily dosing was noninferior to twice daily dosing, since remission rates were comparable across both treatment groups. However, since our study showed clear superiority of once daily dosing, it is important that differences in mesalamine formulations and clinical trial design are considered when comparing efficacy results across studies.

As the improvement in maintenance of remission in the OD group was an unexpected finding, the study was not designed to assess potential influencing factors. Post-hoc analyses revealed no effect of patient variables such as age and gender on remission rates and time to remission, nor any effect of duration or type of disease (left-sided vs pancolitis).

One reason for superior maintenance of remission with the OD regimen may be an effect of higher absolute topical drug concentrations resulting in better pharmacologic control of inflammation. However, we can only speculate on this as peak luminal concentrations were not measured. A recent study of once daily vs 3 times daily mesalamine (Salofalk®) granules (Dr Falk Pharma, Freiburg, Germany) in active UC hypothesized that once daily dosing may lead to higher peak luminal concentrations, particularly in the distal colon.[18] However, studies in healthy volunteers have shown that once daily and twice daily dosing of ethylcellulose-coated mesalamine result in comparable pharmacokinetic properties,[15] and no differences in urinary, fecal, or rectal tissue were observed with once vs 3 times daily dosing in a further study of prolonged-release mesalamine.[14] Although there are limitations of extrapolating healthy volunteer data to patients with active UC, because of differences in intestinal transit, luminal pH, and epithelial permeability,[14] mesalamine pharmacokinetics and rectal tissue concentrations in healthy volunteers are believed to be similar to those in quiescent UC.[27]

Previous studies have indicated that optimized adherence to UC medication is an important predictor of patient outcome.[19,21,23] In our study, compliance rates, as measured by medication use, were not significantly different between the 2 treatment groups. Although one may expect improved adherence when taking medicines once daily compared with twice

daily, this was not confirmed in our study, and only a numerical difference was seen. However, this does not preclude the possibility of improved compliance. This study was not powered to detect small statistically significant differences in compliance, though VAS scores indicated that adherence was significantly improved in the OD group. Using the VAS method might be a more sensitive way of detecting differences, but is clearly less appropriate for their precise quantification. It has previously been reported that there can be a discrepancy between patient-reported compliance and that shown by urinary testing.[22] Assessment of compliance in an appropriately designed study may therefore be warranted to more accurately evaluate any differences between once and twice daily dosing, perhaps employing more rigorous methods, such as urinary drug excretion.

It is nevertheless possible that the observed improvement in efficacy in the 2 g mesalamine OD group may partly be explained by the numerically improved compliance rate. This is supported by the results of the post-hoc subanalyses. Using a Cox regression model, with compliance per 4-month treatment period used as a time-dependent covariate, the treatment effect of once vs twice daily dosing was not significant, while the effect of compliance was highly significant ($P < .0001$). This indicates that improved efficacy with once daily dosing was at least partly related to improved compliance. The higher acceptability of the once daily regimen may also explain the numerically improved compliance rates.

Patient withdrawals and tolerability of study medication were comparable across the 2 treatment groups, suggesting that a reduction from twice to once daily dosing does not result in an increased risk of disease flare or an increase in adverse events that might affect patient continuation with treatment. Although the incidence of adverse events was slightly higher in the OD group, the differences were not statistically significant, and the nature of the events was typical of those experienced in this patient population.

In conclusion, this study clearly shows that a once daily regimen of prolonged-release mesalamine 2 g sachets is at least as effective as, and even superior to, the reference twice daily mesalamine 1 g regimen in maintaining clinical remission in patients with mild to moderate quiescent UC. In addition, prolonged-release mesalamine 2 g OD was well tolerated and more acceptable to patients. These findings suggest that once daily treatment could be offered as a first choice regimen to patients. Indeed, the availability of treatments that can be taken once daily allows increased flexibility to tailor therapy according to patient preference and lifestyle and may also have the potential to enhance compliance.

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Conflicts of Interest

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