Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared with 2.4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: The ASCEND I trial

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BACKGROUND: Delayed-release oral mesalamine 2.4 g/day to 4.8 g/day has been shown to be effective in treating mildly to moderately active ulcerative colitis (UC), but it is unknown whether an initial dose of 4.8 g/day is more effective than 2.4 g/day in patients with mildly to moderately active UC and in the subgroup with moderate disease.

PATIENTS AND METHODS: A six-week, multicentre, randomized, double-blind, controlled trial assessing the safety and clinical efficacy of a new dose (ASCEND I) of medication randomly assigned 301 adults with mildly to moderately active UC to delayed-release oral mesalamine 2.4 g/day (400 mg tablet [n=154]) or 4.8 g/day (800 mg tablet [n=147]). The primary efficacy end point was overall improvement (ie, treatment success), defined as complete remission or response to therapy from baseline to week 6. Primary safety end points were adverse events and laboratory evaluations. Data were also analyzed separately for the prespecified subgroup of patients with moderate UC at baseline.

RESULTS: Treatment success was not statistically different between the treatment groups at week 6; 51% of the group (77 of 150) who received delayed-release oral mesalamine 2.4 g/day and 56% of the group (76 of 136) who received 4.8 g/day reached the efficacy end point (P=0.441). Among the moderate disease subgroup, however, the higher initial dose was more effective; 57% of patients (53 of 93) given delayed-release oral mesalamine 2.4 g/day and 72% of patients (55 of 76) given 4.8 g/day achieved treatment success (P=0.0384). Both regimens were well tolerated.

CONCLUSIONS: Delayed-release oral mesalamine is an effective and well-tolerated initial therapy in patients with mildly to moderately active UC, and a 4.8 g/day dose may enhance treatment success rates in patients with moderate disease compared with mesalamine 2.4 g/day.

Key Words: *Delayed release; Inflammatory bowel disease; Mesalamine; Ulcerative colitis*

La prise de 4,8 g/jour (comprimés de 800 mg) de mésalamine orale à libération retardée par rapport à 2,4 g/jour (comprimés de 400 mg) pour le traitement de la colite ulcéreuse dont l'activité est légère à modérée : L'essai ASCEND I

HISTORIQUE : La prise de 2,4 g/jour à 4,8 g/jour de mésalamine orale à libération retardée est efficace dans le traitement de la colite ulcéreuse (CU) dont l'activité est légère à modérée, mais on ne sait pas si une dose initiale de 4,8 g/jour est plus efficace qu'une dose de 2,4 g/jour chez ces patients ainsi que chez ceux dont la maladie est modérée.

PATIENTS ET MÉTHODOLOGIE : Dans le cadre d'un essai multicentre aléatoire et contrôlé à double insu de six semaines (ASCEND I), on a réparti de manière aléatoire 301 adultes atteints d'une colite ulcéreuse dont l'activité était légère à modérée entre 2,4 g/jour (comprimés de 400 mg, [n=154]) et 4,8 g/jour (comprimés de 800 mg, [n=147]) de mésalamine orale à libération retardée. Le paramètre ultime d'efficacité primaire était l'amélioration globale (c'est-à-dire le succès du traitement), défini comme une rémission ou une réponse complète au traitement entre le début du traitement et la semaine 6. Les paramètres ultimes d'efficacité primaire étaient les réactions indésirables et les évaluations de laboratoire. Les données étaient également analysées séparément dans le sous-groupe de patients précisés d'avance, dont l'activité de la CU était modérée au début du traitement.

RÉSULTATS : Le succès du traitement n'était pas statistiquement significatif entre les groupes de traitement à la semaine 6; 51 % du groupe (77 sur 150) qui avaient reçu 2,4 g/jour de mésalamine orale à libération retardée et 56 % du groupe (76 sur 136) qui en avaient reçu 4,8 g/jour ont atteint le paramètre ultime d'efficacité (P=0,441). Au sein du sous-groupe de maladie modérée, cependant, la dose initiale plus élevée était plus efficace : 57 % des patients (53 sur 93) qui avaient reçu 2,4 g/jour de mésalamine orale à libération retardée et 72 % du groupe (55 sur 76) qui en avaient reçu 4,8 g/jour ont profité du succès du traitement (P=0,0384). Les deux posologies étaient bien tolérées.

CONCLUSIONS : La mésalamine orale à libération retardée est un traitement initial bien toléré chez les patients atteints d'une UC dont l'activité est légère à modérée, et une dose de mésalamine de 4,8 g/jour peut améliorer les taux de réussite du traitement chez les patients atteints d'une maladie modérée par rapport à ceux qui en prennent 2,4 g/jour.

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Ulcerative colitis (UC) is a chronic inflammatory disorder of the colon of unknown etiology. It affects men and women equally, with an initial peak during the third decade of life, followed by a plateau and, possibly, a second peak in later years (1,2). UC is characterized by a continuous pattern of inflammation that may either be isolated to the rectum or extend proximally to involve the entire colon (3). Although the condition is chronic and medically incurable, alternating sporadic flares and intermittent periods of drug-induced or spontaneous remission, or quiescent disease, typify the clinical course of UC. The severity of UC is classified as mild, moderate, severe or fulminant, based primarily on clinical symptoms. It is estimated that approximately 71% of patients present with moderately active UC, whereas 20% present with mildly active disease (2).

Initial therapy for patients with mildly to moderately active UC typically consists of a 5-aminosalicylic acid (5-ASA) compound (3). Depending on the location and extent of disease, oral or rectal therapies may be used individually or in combination. The clinical benefit tends to be dose related. The content and the formulation delivering 5-ASA to specific areas of the gastrointestinal tract differentiate the marketed, orally administered 5-ASA products, which include sulfasalazine, mesalamine, balsalazide and olsalazine. Drug release profiles reflect differences in drug delivery systems, such as pH-dependent release associated with a resin coating, timed-release or release of 5-ASA after splitting by bacterial enzymes (4-6).

Delayed-release mesalamine is formulated with a Eudragit-S (Asacol, Procter & Gamble Pharmaceuticals, USA) acrylic-based resin coating that disintegrates at a pH of at least 7, delivering 5-ASA beginning at the terminal ileum and continuing throughout the colon (5,6). Clinical trials have demonstrated that delayed-release or sustained-release mesalamine, at doses of 2.0 g/day to 4.8 g/day, can effectively treat mildly to moderately active UC (7-9). In addition to the 400 mg delayed-release oral mesalamine (Asacol) tablet, an 800 mg tablet has now been approved in Canada, with which the treatment of moderately active UC can be initiated with delayed-release oral mesalamine at 4.8 g/day (10). Because patient choice and convenience are important factors in determining patient satisfaction with a medication (11), an 800 mg tablet may provide a desirable alternative treatment option for some patients who are prescribed these higher doses.

The vast majority of patients presenting with active UC have either mildly or moderately active disease, suggesting the use of an initial delayed-release oral mesalamine dose of 2.4 g/day to 4.8 g/day (3,4). Previously conducted studies indicate that a delayed-release oral mesalamine dose of 2.4 g/day or higher would be effective in patients with mildly to moderately active disease. However, it was unknown whether initial therapy with mesalamine at a dose of 4.8 g/day would be more effective than a dose of 2.4 g/day in patients with mildly to moderately active UC or in the subgroup of patients with moderately active UC.

Two clinical trials assessing the safety and clinical efficacy of a new dose (ASCEND) of 5-ASA (ASCEND I and II) were conducted to evaluate the efficacy and safety of the new 800 mg Asacol tablet in the treatment of active UC. ASCEND I, the results of which are presented here, was a randomized, double-blind, controlled trial comparing the efficacy and safety of Asacol 4.8 g/day (800 mg tablet) with that of Asacol 2.4 g/day (400 mg tablet) in patients with mildly to moderately active UC. The parallel ASCEND II trial primarily enrolled patients with moderately active UC to receive either Asacol 4.8 g/day (800 mg tablets) or Asacol 2.4 g/day (12).

PATIENTS AND METHODS

The present six-week multicentre, randomized, double-blind, active-controlled trial was conducted at 41 centres across Canada and the United States between February 2001 and November 2002. The trial enrolled patients with mildly to moderately active UC, either newly diagnosed or with a flare of previously diagnosed disease. The institutional review board or ethics committee at each site approved the protocol, and all patients gave written informed consent.

Inclusion and exclusion criteria

Eligibility criteria included age of 18 to 75 years; confirmed UC with disease extent (proctitis to pancolitis) confirmed by endoscopy or radiography within 24 months before the baseline visit; and mildly to moderately active disease at entry, with a physician's global assessment (PGA) score of 1 or 2 at baseline (7,8,12). Exclusion criteria included short bowel syndrome; intolerance of or allergy to salicylates or 5-ASA compounds; current renal or hepatic disease; current alcohol or drug abuse; medical contraindication to study participation; blood urea nitrogen or serum creatinine more than 1.5 times the upper limit of normal; hepatic enzymes more than 2.0 times the upper limits of normal; positive stool examination for bacterial pathogens, ova and parasites, or *Clostridium difficile*; use of 5-ASA-containing products by any route from which a total dose of more than 1.6 g/day was available within seven days before screening; use of corticosteroids (oral, intravenous, intramuscular or rectal) within one month before the baseline visit; use of any topical rectal therapy within one week before screening; use of immunomodulatory drugs within three months before the baseline visit; use of antibiotics (other than topical), nicotine patches, any product containing fish oils, acetylsalicylic acid (except for a cardioprotective dose of no more than 325 mg, or nonsteroidal anti-inflammatory drugs within one week before screening; use of antidiarrheal and/or antispasmodic medications after the screening visit; treatment with any experimental or investigational medication within one month before the baseline visit; and pregnancy or lactation.

Prohibited medications during the study were acetylsalycilic acid (other than a maximum dose of 325 mg/day for cardioprotective reasons), nonsteroidal anti-inflammatory drugs, other mesalamine-containing products, corticosteroids, immunomodulatory agents, metronidazole; antibiotics (other than topical antibiotics) for more than 10 days throughout the study, topical rectal therapies, antidiarrheal and antispasmodic medications, nicotine patches, products containing fish oils, and any investigational or marketed drug that could interfere with evaluation of the study medication.

Patients were screened according to inclusion and exclusion criteria within seven days before the baseline visit.

Random assignment and blinding

Eligible patients were randomly assigned at the baseline visit in a 1:1 ratio at each site to receive either delayed-release oral mesalamine 2.4 g/day (400 mg Asacol tablet) or delayed-release oral mesalamine 4.8 g/day (investigational 800 mg Asacol tablet), and were monitored for six weeks. Permutated blocks of four were used to randomly assign treatments to patients. The

random assignment scheme was generated for each study centre. No demographic or baseline disease characteristics were used as stratification variables for random assignment.

A double-blind study design was used, with both patients and investigators blinded to treatment assignment. Patients randomly assigned to delayed-release oral mesalamine 2.4 g/day received two 400 mg tablets and two placebo tablets identical to the 800 mg tablets three times per day (morning, midday and evening), and patients randomly assigned to delayed-release oral mesalamine 4.8 g/day received two 800 mg tablets and two placebo tablets identical to the 400 mg tablets three times per day (morning, midday and evening).

Participant flow and follow-up examinations

Patients were assessed at study visits at baseline (week 0), week 3 and study completion (week 6). Sigmoidoscopy was performed at screening, and at weeks 3 and 6. Study participants recorded data for stool frequency and rectal bleeding, and patient's functional assessment (PFA) was done by daily telephone contact with an integrated voice-response system. The investigator reviewed these data; assigned scores for each measurement determined during patient visits at weeks 0, 3 and 6, and determined a PGA score based on those clinical scores, the sigmoidoscopy score, and the investigator's clinical judgment.

Patients completed the 32-question Inflammatory Bowel Disease Questionnaire (IBDQ) at each visit, and total quality of life (QOL) scores and the four subcategory scores (bowel, systemic, social and emotional) were calculated at each visit. Medication compliance was assessed at weeks 3 and 6. Blood samples were obtained from each patient at weeks 0, 3 and 6 to estimate plasma 5-ASA and *N*-acetyl 5-ASA (*N*-Ac-5-ASA), its major metabolite.

Adverse events and concomitant medications were also documented, and samples were collected for laboratory evaluation at each visit. Safety evaluations included vital signs, physical examination, hematology, serum biochemistry and urinalysis.

Analysis and statistical methods

The primary efficacy end point was overall improvement at week 6 in patients with mildly to moderately active UC. Secondary efficacy end points included the proportion of patients who improved from baseline at week 3 and the percentage of patients whose clinical assessment scores (stool frequency, rectal bleeding, sigmoidoscopy scores, PFA scores and PGA scores) improved from baseline scores at weeks 3 and 6. Tertiary end points analyzed included improvement in QOL from baseline to weeks 3 and 6, and time to symptom relief (stool frequency, rectal bleeding or both). Primary safety end points included reported adverse events and clinical laboratory evaluations. The safety analysis included data for all randomly assigned patients. Efficacy and safety data were also analyzed separately for the prespecified subgroup of patients with moderately active UC (PGA=2) at baseline.

Overall improvement or treatment success was defined as either complete remission or a clinical response to therapy. Complete remission was defined as normal stool frequency, no rectal bleeding, a PFA score of 0 (generally healthy), normal endoscopy findings and a PGA score of 0 (quiescent disease activity). A clinical response to therapy was defined as a decrease in the PGA score of at least one point from baseline, plus improvement in at least one other clinical assessment parameter (stool frequency, rectal bleeding, PFA or endoscopy findings) and no worsening in any of the other clinical assessments.

The PGA score was used to assess disease severity and efficacy. The PGA, a four-point score, was a composite of the scores used to assess stool frequency, rectal bleeding, PFA, endoscopic findings and the investigator's clinical judgment. The PGA score corresponded to quiescent (score 0), mild (score=1), moderate (score=2) or severe (score=3) disease activity. The PGA score was used to classify the disease activity for all randomly assigned patients at baseline, week 3 and week 6 to permit comparison of PGA scores between the two treatment groups. At baseline (ie, random assignment), there were no significant differences in PGA scores between the two treatment groups (P=0.3582) for all randomly assigned patients. A comparison of PGA scores was not possible for the moderately active disease subgroup, because all patients had a PGA score of 2; a statistical comparison would have been irrelevant. The PFA was also rated on a four-point scale, indicating generally well (score=0) to terrible (score=3).

Subgroup analyses were conducted for the primary efficacy end point of overall improvement using the intention-to-treat (ITT) population to evaluate the consistency of the effect of treatment across various patient populations. The association between treatment and outcome was examined for treatment effect and consistency of effect for demographic characteristics such as age, sex, ethnic background and smoking status; disease history, including extent of disease, length of disease history, hydrogen blocker and proton pump inhibitor use, prior UC medication use, sulfasalazine intolerance and relapse frequency; and baseline disease activity measures, including PGA, stool frequency, rectal bleeding, PFA and sigmoidoscopy scores.

The primary efficacy ITT analysis was the primary analysis, and included all randomly assigned patients with mildly to moderately active disease who ingested at least one dose of drug and whose treatment outcome could be determined. The sensitivity analysis (week 6 outcome set to treatment failure or to last known outcome) included patients whose outcome at week 6 could not be determined and therefore were not included in the primary efficacy ITT analysis. Per-protocol analyses were also performed. Randomly assigned patients who completed the study were classified as either treatment successes (complete or partial improvement) or failures. Randomly assigned patients who withdrew due to adverse events or lack of treatment effect were classified as treatment failures. The χ^2 test was used to determine the overall treatment effect, and 95% CIs for treatment differences between the two groups were provided. Subgroup analyses of demographic characteristics, disease history and disease activity measures to assess the consistency of treatment effect were performed using the Cochran-Mantel-Haenszel χ^2 test. Changes from baseline in total and subcategory IBDQ scores for both treatment groups were analyzed using the paired *t* test to examine the within-group treatment effect, and Wilcoxon's signed rank test was used to compare the between-group treatment effect.

The sample size calculation was based on the assumption that the true rate of improvement was 40% for the group receiving delayed-release oral mesalamine 2.4 g/day and 60% for the group receiving delayed-release oral mesalamine 4.8 g/day. To detect a 20% difference between these groups with 90% power, 280 patients with mildly to moderately active UC were required to complete the study.

TABLE 1
Baseline demographics and ulcerative colitis treatment history of all randomly assigned patients

	Delayed-release oral mesalamine dose				
	Patients given 2.4 g/day (n=154)		Patients given 4.8 g/day (n=147)		
Parameter	n	%	n	%	P*
Mean age, years	43.5	–	45.9	–	0.1237
18–64	141	91.6	133	90.5	
≥65	13	8.4	14	9.5	
Sex					0.3209
Male	75	48.7	80	54.4	
Female	79	51.3	67	45.6	
Ethnic background					0.9873
Caucasian	122	79.2	116	78.9	
Black	18	11.7	18	12.2	
Hispanic	10	6.5	9	6.1	
Other	4	2.6	4	2.7	
Smoking history					0.4822
Never smoked	78	50.6	69	46.9	
Used to smoke	66	42.9	63	42.9	
Currently smoke	10	6.5	15	10.2	
Disease extent					0.7824
Proctitis	25	16.2	29	19.7	
Proctosigmoiditis	45	29.2	38	25.9	
Left-sided colitis	45	29.2	46	31.3	
Pancolitis	39	25.3	34	23.1	
Length of disease history, years					0.1430
<1	62	40.3	50	34.0	
1–5	25	16.2	40	27.2	
>5–10	28	18.2	23	15.6	
>10	38	24.7	33	22.4	
Unknown	1	0.6	1	0.7	
Prior treatment					
Steroids (oral or IV)	51	33.1	43	29.3	0.4695
Immunomodulators	7	4.5	7	4.8	0.9290
Sulfasalazine	57	37.0	43	29.3	0.1530
Sulfa-free oral 5-ASAs	61	39.6	70	47.6	0.1612
Rectal therapy	67	43.5	60	40.8	0.6366
Intolerant to sulfasalazine					0.5372
Yes	8	14.0	8	18.6	
No	49	86.0	35	81.4	
Relapse frequency					0.3979
Newly diagnosed	55	35.7	43	29.3	
More than once per month	14	9.1	20	13.6	
Once every 6 months	20	13.0	14	9.5	
Once every 6-12 months	26	16.9	32	21.8	
Less than once per year	39	25.3	38	25.9	

**P value determined using χ^2 test or t test, with significance defined as P≤0.05. 5-ASA 5-aminosalicylic acid; IV Intravenous*

RESULTS

Patient characteristics

A total of 301 patients were studied, with 154 randomly assigned to delayed-release oral mesalamine 2.4 g/day and 147 randomly assigned to delayed-release oral mesalamine 4.8 g/day. Baseline patient characteristics were similar between the two treatment groups (Table 1). An overview of patient disposition is provided in Figure 1. The primary efficacy ITT analysis included 150 patients assigned to delayed-release oral mesalamine 2.4 g/day and 136 patients assigned to delayed-release oral mesalamine 4.8 g/day. Patients who were not analyzed at week 6 included those who completed the study but were missing at least one symptom score, as well as those who did not complete the study due to voluntary withdrawal or protocol deviation.

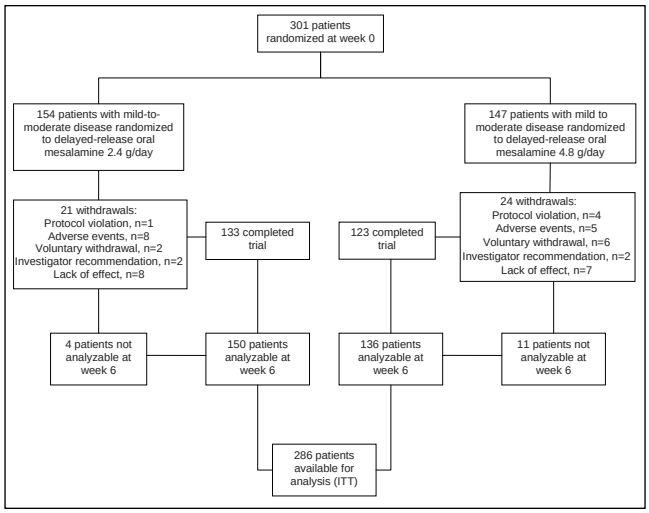

Figure 1) *Patient disposition. Patients who could not be analyzed at week 6 included those who completed week 6 but were missing at least one symptom score (one patient in each treatment group), and patients who did not complete the study due to voluntary withdrawal (two patients in the 2.4 g/day delayed-release oral mesalamine group and six patients in the 4.8 g/day group) or to protocol deviations (one patient in the 2.4 g/day delayed-release oral mesalamine group and four patients in the 4.8 g/day group). ITT Intention-to-treat*

Efficacy outcomes: All patients

The ITT analysis for the primary end point indicated that the percentage of patients with mildly to moderately active UC and treatment success at six weeks was not statistically different between the two treatment groups (Figure 2). At week 6, 51% of the group (77 of 150) receiving delayed-release oral mesalamine 2.4 g/day and 56% of the group (76 of 136) receiving delayed-release oral mesalamine 4.8 g/day experienced overall improvement (P=0.441), and at week 3, 42% (63 of 150) and 39% (53 of 137) of these groups, respectively, experienced overall improvement (P=0.5677). Sensitivity analyses using missing outcomes set to treatment failure and last observation carried forward found no statistical differences in treatment outcomes between the groups receiving delayed-release oral mesalamine 2.4 g/day and 4.8 g/day.

Among patients who were considered to have treatment success, a greater number of patients in the delayed-release oral mesalamine 4.8 g/day group (35 of 76, 46%) had a complete response than in the delayed-release oral mesalamine 2.4 g/day group (30 of 77, 38%). However, the differences in the secondary end points of PGA, stool frequency, rectal bleeding, PFA and sigmoidoscopy scores were not significantly different between the groups at weeks 3 or 6.

The median time for patients to return to normal stool frequency and for rectal bleeding to resolve was not statistically different between the treatment groups. However, the median time for both clinical assessments (ie, rectal bleeding and stool frequency) to resolve and return to normal was shorter in the

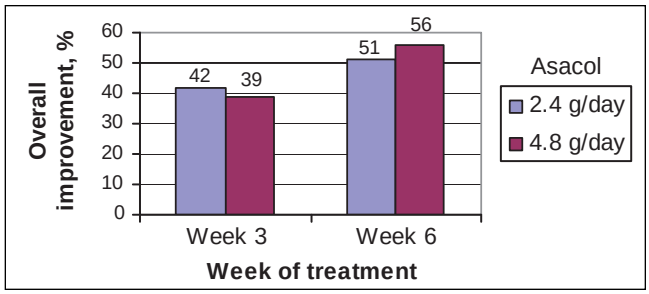

Figure 2) *Asacol (Proctor & Gamble Pharmaceuticals, USA) treatment outcomes at weeks 3 and 6 in all patients with mildly to moderately active ulcerative colitis*

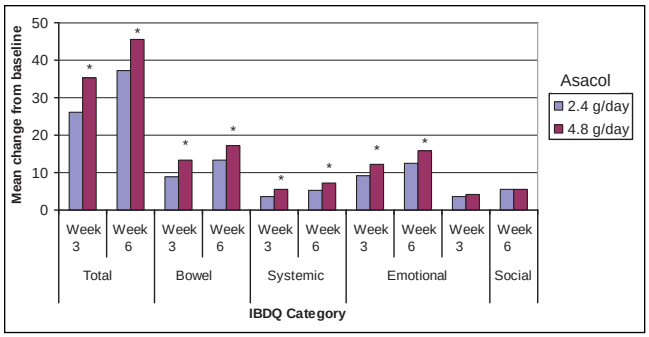

Figure 3) *The total Inflammatory Bowel Disease Questionnaire (IBDQ) scores and all subcategory scores for patients with mildly to moderately active ulcerative colitis improved significantly from baseline to weeks 3 and 6 in both treatment groups (Asacol, Proctor & Gamble Pharmaceuticals, USA). *Significant difference in the between-treatment comparison using Wilcoxon's signed rank test (P≤0.05)*

patients who received delayed-release oral mesalamine 4.8 g/day (for 15 days) than in patients who received delayed-release oral mesalamine 2.4 g/day (for 24 days) (P=0.0719).

The total IBDQ scores and all subcategory scores for patients with mildly to moderately active UC improved significantly from baseline to weeks 3 and 6 in both treatment groups. The total IBDQ score and all subcategory scores, with the exception of social score, showed a statistically greater improvement among patients who received delayed-release oral mesalamine 4.8 g/day than among those who received delayed-release oral mesalamine 2.4 g/day (Figure 3).

An analysis of outcomes by demographic, disease history and disease extent variables identified homogenous treatment effects for all subgroup variables except baseline disease severity, prior use of corticosteroids, extent of disease, stool frequency score and PFA score. For these subgroup parameters, the treatment effects suggested that patients with more severe disease may have responded better than patients with less severe disease. Patients who had used steroids previously had a higher response rate than those who had not. The rates of overall improvement in patients with disease extent limited to the left colon (including proctitis, proctosigmoiditis and left-sided colitis) and those with pancolonic involvement were greater at week 6 in those who received delayed-release oral mesalamine 4.8 g/day than in those who received delayed-release oral mesalamine 2.4 g/day, but these differences were not significant. In all subgroup variables analyzed, patients who received delayed-release oral mesalamine 4.8 g/day showed a trend toward greater overall improvement than patients who received delayed-release oral mesalamine 2.4 g/day. The per-protocol primary efficacy analysis was not statistically significant, although the per-protocol rectal bleeding score, a secondary efficacy outcome, was statistically significant.

Efficacy outcomes: Moderate disease subgroup

Across the study population at baseline, 121 patients had mildly active (PGA=1) and 180 patients had moderately active (PGA=2) disease. The primary efficacy analysis for the moderately active subgroup included 96 patients who received delayed-release oral mesalamine 2.4 g/day and 84 patients who received delayed-release oral mesalamine 4.8 g/day. Baseline patient characteristics in the moderately active disease subgroup were similar in both treatment groups (Table 2). Premature withdrawals in the moderate disease subgroup were primarily due to a lack of treatment effect or to adverse events; those included 18 patients (19%) who received delayed-release oral mesalamine 2.4 g/day and 17 patients (20%) who received delayed-release oral mesalamine 4.8 g/day.

At week 6, 57% of patients (53 of 93) who received delayed-release oral mesalamine 2.4 g/day and 72% of patients (55 of 76) who received delayed-release oral mesalamine 4.8 g/day achieved overall improvement (Figure 4). The difference in overall improvement was 15% (95% CI 1.16% to 29.6%, P=0.0384). Improvement in individual clinical assessments was greater at weeks 3 and 6 in the group who received delayed-release oral mesalamine 4.8 g/day, but most differences were not significant. However, the PGA and sigmoidoscopy scores improved significantly at week 6 in the 4.8 g/day group compared with the 2.4 g/day group. Analysis of outcomes by extent of disease demonstrated comparable treatment effects regardless of the extent of disease.

Although not statistically significant, the median time for rectal bleeding to resolve in patients with moderate disease was shorter in the group that received delayed-release oral mesalamine 4.8 g/day (for nine days) than in the group that received delayed-release oral mesalamine 2.4 g/day (for 13 days) (P=0.0930). The median times to symptom resolution (stool frequency, rectal bleeding and both) are shown in Table 3.

The improvement in IBDQ scores was statistically significant (Figure 5). At week 3, the change in total IBDQ score was in favour of the delayed-release oral mesalamine 4.8 g/day group (P=0.0519). A statistically significant improvement in bowel (P=0.0167) and systemic (P=0.0450) subscores was seen in the delayed-release oral mesalamine 4.8 g/day treatment group. At week 6, statistically significant improvements from baseline were seen in the total IBDQ score and in all subcategory scores in both treatment groups (P<0.0001), and significantly greater improvements in the total score (P=0.0336) and bowel subcategory score were seen at week 6 in the group that received delayed-release oral mesalamine 4.8 g/day than in the group that received delayed-release oral mesalamine 2.4 g/day.

Safety outcomes: All patients

The incidence of adverse events was similar in both treatment groups, as were the most frequently reported adverse events (Table 4). Eight patients (5%) in the 2.4 g/day treatment group and five patients (3%) in the 4.8 g/day treatment group discontinued treatment because of an adverse event. Serious adverse events occurred in three patients (2%) in the delayed-release oral mesalamine 2.4 g/day group and one patient (1%) in the 4.8 g/day group; all four patients had moderately active UC at

TABLE 2
Baseline demographics and ulcerative colitis treatment history of patients with moderately active ulcerative colitis

	Delayed-release oral mesalamine dose				
	Patients given 2.4 g/day (n=96)		Patients given 4.8 g/day (n=84)		
Parameter	n	%	n	%	P*
Mean age, years	43.0	1.39	45.4	1.53	0.2637
18–64	88	91.7	76	90.5	
≥65	8	8.3	8	9.5	
Height, cm	169.0	1.00	169.7	1.21	0.6791
Weight, kg	76.6	1.56	78.2	1.74	0.4978
Ethnic background					0.8781
Caucasian	74	77.1	62	73.8	
Black	12	12.5	12	14.3	
Asian (Indian)	1	1.0	2	2.4	
Hispanic	8	8.3	7	8.3	
Multiracial or other	1	1.0	1	1.2	
Sex					0.8107
Male	44	45.8	40	47.6	
Female	52	54.2	44	52.4	
Smoking history					0.1432
Never smoked	50	52.1	38	45.2	
Used to smoke	42	43.8	36	42.9	
Currently smoke	4	4.2	10	11.9	
Disease extent					0.8676
Proctitis	15	15.6	11	13.1	
Proctosigmoiditis	26	27.1	22	26.2	
Left-sided colitis	30	31.3	31	36.9	
Pancolitis	25	26.0	20	23.8	
Length of disease history, years				0.1475	
<1	37	38.5	23	27.4	
1–5	17	17.7	26	31.0	
>5–10	16	16.7	15	17.9	
>10	26	27.1	19	22.6	
Unknown	0	0.0	1	1.2	
Prior treatment					
Steroids (oral or IV)	33	34.4	30	35.7	0.8509
Immunomodulators	7	7.3	4	4.8	0.4796
Sulfasalazine	36	37.5	25	29.8	0.2739
Sulfa-free oral 5-ASAs	36	37.5	43	51.2	0.0648
Rectal therapies	44	45.8	38	45.2	0.9362
Intolerant to sulfasalazine					0.8298
Yes	5	13.9	3	12.0	
No	31	86.1	22	88.0	
Relapse frequency					0.5389
Newly diagnosed	32	33.3	19	22.6	
More than once per month	9	9.4	12	14.3	
Once every 6 months	8	8.3	9	10.7	
Once every 6–12 months	17	17.7	16	19.0	
Less than once per year	30	31.3	28	33.3	

**P value determined using χ^2 test or t test, with significance defined as P≤0.05. 5-ASA 5-aminosalicylic acid; IV Intravenous*

baseline. No deaths occurred during the study. No clinically significant changes in laboratory values from baseline were seen in either treatment group, and no significant differences were seen between treatment groups. Additionally, the safety profile was similar in subgroups with mild and moderate disease.

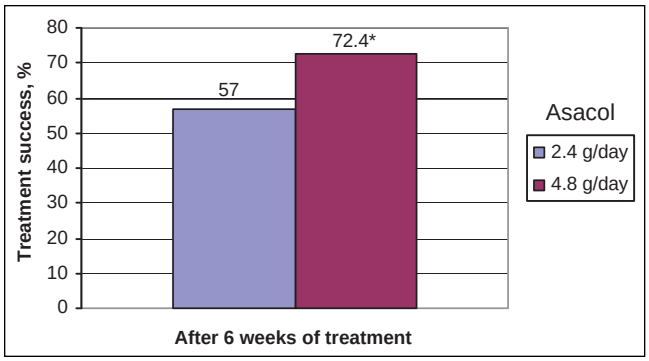

Figure 4) *Treatment success in the subgroup of patients with moderately active ulcerative colitis who were administered delayed-release oral mesalamine (Asacol, Proctor & Gamble Pharmaceuticals, USA) at a dose of either 2.4 g/day or 4.8 g/day. *Significant difference in between-treatment comparison using Wilcoxon's signed rank test (P=0.0384)*

TABLE 3
Median days to symptom relief for patients with moderately active disease (physician's global assessment score = 2) at baseline

	Delayed-release oral mesalamine dose				
	2.4 g/day (N=96)		4.8 g/day (N=84)		Log-rank
Symptom	n	Median	n	Median	P*
Abnormal stool frequency	78	18.0	70	14.0	0.5380
Rectal bleeding	73	13.0	65	9.0	0.0930
Both	65	28.0	56	20.0	0.1316

'N' indicates the number of patients in the treatment group and 'n' indicates the number of patients in each treatment group with a screening score >0 for a specified symptom. Symptom relief was defined as a total resolution of the symptom (ie, score = 0). Time to symptom relief was defined as the number of days between the first day of dosing and the first day of symptom relief

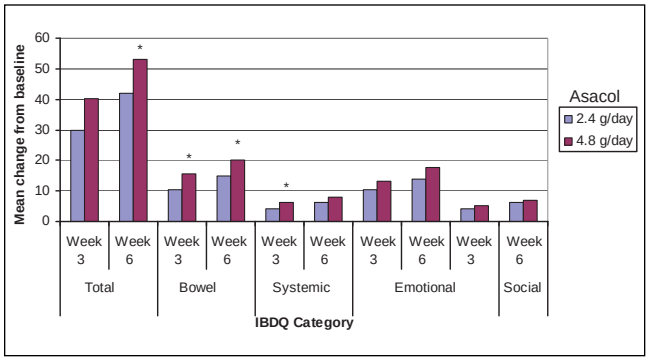

Figure 5) *Mean change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) scores at weeks 3 and 6 in the subgroup of patients with moderately active ulcerative colitis who were administered delayed-release oral mesalamine (Asacol, Proctor & Gamble Pharmaceuticals, USA) at doses of either 2.4 g/day or 4.8 g/day. *Significant difference in between-treatment comparison using Wilcoxon's signed rank test (P≤0.05)*

Safety outcomes: Moderate disease subgroup

Adverse event rates in patients with moderate disease were similar in the 2.4 g/day and 4.8 g/day groups (Table 5), as were the most frequently reported adverse events. Eight patients in the 2.4 g/day group and five patients in the 4.8 g/day group

TABLE 4
Summary of adverse events (AEs) for all randomly assigned patients

	Delayed-release oral mesalamine dose					
	2.4 g/day (N=154)		4.8 g/day (N=147)		Total (N=301)	
Parameter	n	%	n	%	n	%
Patients with AEs*	60	39.0	48	32.7	108	35.9
Patients withdrawn due to AEs	8	5.2	5	3.4	13	4.3
Patient deaths	0	0.0	0	0.0	0	0.0
Number of AEs reported	107		99		206	
AEs assessed as†						
Mild	58	54.2	39	39.4	97	47.1
Moderate	40	37.4	49	49.5	89	43.2
Severe	9	8.4	11	11.1	20	9.7
AEs assessed as†						
Not likely related to study drug	79	73.8	58	58.6	137	66.5
Possibly related to study drug	26	24.3	32	32.3	58	28.2
Probably related to study drug	2	1.9	9	9.1	11	5.3
Number of serious AEs reported	8		1		9	
Mean number of AEs per patient‡	0.7		0.7		0.7	
Mean number of AEs among patients with AEs§	1.8		2.1		1.9	
Mean number of AEs per patient per month of exposure¶	1.44		1.66		1.54	

*'N' indicates the number of patients in the treatment group, and 'n' and '%' indicate the number and percentage (n/N × 100) of patients in the specified category and treatment group; *Patients who experienced one or more AEs in the category were counted only once; †Percentage based on the number of AEs reported; ‡Number of AEs reported/N; §Number of AEs reported/number of patients with AEs; ¶Based on a 30-day month*

TABLE 5
Summary of adverse events (AEs) in the moderate disease subgroup

	Delayed-release oral mesalamine dose					
	2.4 g/day (N=96)		4.8 g/day (N=84)		Total (N=180)	
Parameter	n	%	n	%	n	%
Patients with AEs*	37	38.5	27	32.1	64	35.6
Patients withdrawn due to AEs	8	8.3	5	6.0	13	7.2
Patient deaths	0	0.0	0	0.0	0	0.0
Number of AEs reported	74		57		131	
AEs assessed as†						
Mild	35	47.3	20	35.1	55	42.0
Moderate	31	41.9	28	49.1	59	45.0
Severe	8	10.8	9	15.8	17	13.0
AEs assessed as†						
Not likely related to study drug	52	70.3	24	42.1	76	58.0
Possibly related to study drug	21	28.4	24	42.1	45	34.4
Probably related to study drug	1	1.4	9	15.8	10	7.6
Number of serious AEs reported	8		1		9	
Mean number of AEs per patient‡	0.8		0.7		0.7	
Mean number of AEs among patients with AEs§	2.0		2.1		2.0	
Mean number of AEs per patient per month of exposure¶	1.75		1.81		1.77	

*'N' indicates the number of patients in a treatment group and 'n' and '%' indicate the number and percentage (n/N × 100) of patients in the specified category and treatment group. *Patients who experienced one or more AEs in the category were counted only once; †Percentage based on the number of AEs reported; ‡Number of AEs reported/N; §Number of AEs reported/number of patients with AEs; ¶Based on a 30-day month*

discontinued treatment because of an adverse event. Serious adverse events occurred in three patients (3%) in the delayed-release oral mesalamine 2.4 g/day group (uterine fibroids and ovarian cyst; worsening UC; cholecystitis) and one patient (1%) in the delayed-release oral mesalamine 4.8 g/day group (epigastric pain).

5-ASA pharmacokinetics

In all patients with either mildly or moderately active UC, the mean (± SD) plasma 5-ASA concentration at week 6 was 981±1424 ng/mL in the delayed-release oral mesalamine 2.4 g/day group and 1655±1781 ng/mL in the delayed-release oral mesalamine 4.8 g/day group. The mean plasma *N*-Ac-5-ASA concentration at week 6 was 1857±1635 ng/mL for the delayed-release oral mesalamine 2.4 g/day group and 2867±2316 ng/mL in the delayed-release oral mesalamine 4.8 g/day group. Plasma concentrations demonstrated a dose-related increase in both 5-ASA and *N*-Ac-5-ASA in the delayed-release oral mesalamine 4.8 g/day group (800 mg tablet) compared with the delayed-release oral mesalamine 2.4 g/day group (400 mg tablet), with the median values for the 4.8 g/day dose ranging from 1.5 to 2.5 times those for the 2.4 g/day dose. The mean 5-ASA and *N*-Ac-5-ASA week 3 concentrations were similar to the week 6 concentrations for both treatment groups.

DISCUSSION

In patients with mildly to moderately active UC, no statistically significant difference was seen in the treatment outcomes between delayed-release oral mesalamine 2.4 g/day (400 mg tablet) and delayed-release oral mesalamine 4.8 g/day (800 mg tablet) after six weeks of treatment. Previously, Schroeder et al (7) found delayed-release oral mesalamine 4.8 g/day to be significantly more effective than placebo in inducing a complete or partial response in a population with mildly to moderately active UC. Baseline PGA scores indicated that disease activity in this population tended more toward the moderate category. Sninsky et al (8) found delayed-release oral mesalamine 2.4 g/day to be significantly more effective than placebo in a similar population, although baseline disease assessments indicated that this population with more mild than moderate disease. The current study is the first to compare the relative efficacy of these two dose levels in patients with mild to moderate disease.

Although ASCEND I did not demonstrate a statistical difference in treatment success between doses for the entire population, the prespecified efficacy analysis of the moderate disease patient subgroup demonstrated statistically significant improved outcomes for delayed-release oral mesalamine 4.8 g/day compared with delayed-release oral mesalamine 2.4 g/day (72.4% versus 57%; P=0.0384). These results of the ASCEND I subgroup analysis led to an amendment of the ongoing ASCEND II protocol to restrict trial entry and primary analysis to patients with moderate disease only. ASCEND II was a randomized, double-blind, controlled trial comparing the efficacy and safety of delayed-release oral mesalamine 4.8 g/day (800 mg tablet) with delayed-release oral mesalamine 2.4 g/day (400 mg tablet) in a group with primarily moderate disease (12). In the present study, patients with moderately active UC who took delayed-release

oral mesalamine 4.8 g/day had a significantly greater treatment response than comparable patients who took delayed-release oral mesalamine 2.4 g/day (72% versus 59% respectively; P=0.036).

The protocols for ASCEND I and II prespecified criteria for defining mild and moderate disease, but a consensus does not yet exist among clinicians on definitions for these disease severity categories. Developing an optimal approach to initial management of patients with mildly active UC and those with moderately active disease therefore depends on the ability to differentiate these populations on a clinical level in a simple manner. In patients with moderate disease, initiating therapy at a delayed-release oral mesalamine dose of 4.8 g/day may improve response to initial therapy, reducing the need to move to corticosteroids.

In addition to clinical assessments of disease response, management of a UC patient requires a comprehensive assessment of the patient's functioning and overall sense of well-being or QOL. The IBDQ is a reliable tool for measuring health-related QOL in patients with UC. In ASCEND I, the total and subcategory IBDQ scores showed significant improvement from baseline and significantly greater improvement in patients treated with delayed-release oral mesalamine 4.8 g/day than patients treated with delayed-release oral mesalamine 2.4 g/day. Measuring QOL in both clinical practice and investigative trials is important, because a patient's perception of UC may be influenced by his or her psychological status, and how well he or she is feeling may ultimately determine the classification of disease state and influence treatment outcomes.

The results of the ASCEND trials indicate that differentiating between mild and moderate disease may have important clinical implications, especially because approximately 70% of UC patients present with moderate disease (2). Historically, mildly and moderately active UC have been viewed clinically more as a continuum than as separate entities, and the appropriate delayed-release oral mesalamine dose for initial treatment of these patients has been expressed as a range (2.4 g/day to 4.8 g/day) (3). The results of ASCEND I and II demonstrate that patients with moderate disease benefit from an initial delayed-release oral mesalamine dose of 4.8 g/day.

There are several possible explanations as to why the higher dose appeared to be less effective in patients with mild disease. One possibility is that the higher dose is not as well tolerated in patients with mild disease, hence masking a therapeutic benefit. Alternatively, patients with mild disease may have an increased response to placebo, and hence, no statistical difference could be discerned between doses.

Overall adverse event rates were similar in both groups, and the higher delayed-release oral mesalamine dose was not associated with an increased incidence of adverse events. No new or unexpected adverse events were seen, and the most commonly experienced adverse events were those expected with mesalamine (7,8). Delayed-release oral mesalamine doses of 2.4 g/day (400 mg tablet) and 4.8 g/day (800 mg tablet) have comparable safety profiles when administered for the treatment of mildly to moderately active UC for a period of six weeks. The pharmacokinetic data demonstrate findings consistent with pharmacokinetic studies of delayed-release oral mesalamine and other medications containing 5-ASA (6).

CONCLUSIONS

Delayed-release oral mesalamine is both effective and well tolerated in patients with mildly to moderately active UC. In addition, ASCEND I provides preliminary evidence supporting the use of an initial 4.8 g dose to treat patients with moderate disease. The new 800 mg delayed-release oral mesalamine tablet may provide patients with a convenient alternative to the current 400 mg tablet (11).

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