CLINICAL—ALIMENTARY TRACT

Budesonide 9 mg Is at Least as Effective as Mesalamine 4.5 g in Patients With Mildly to Moderately Active Crohn's Disease

ANDREAS TROMM,[*] IVAN BUNGANIČ,[‡] EVA TOMSOVÁ,[§] ZSOLT TULASSAY,[‖] MILAN LUKÁŠ,[¶] JAN KYKAL,[#] MARIAN BÁTOVSKÝ,[**] BOHUMIL FIXA,[‡‡] LIBOR GABALEC,[§§] RIFAAT SAFADI,[‖‖] HEINZ–JOCHEN KRAMM,[¶¶] ISTVÁN ALTORJAY,[##] HANNS LÖHR,[***] IOANNIS KOUTROUBAKIS,[‡‡‡] SIMON BAR–MEIR,[§§§] DAVOR ŠTIMAC,[‖‖‖] ELKE SCHÄFFELER,[****] CHRISTOPH GLASMACHER,[¶¶¶] KARIN DILGER,[###] RALF MOHRBACHER,[###] ROLAND GREINWALD,[###] and the International Budenofalk Study Group

[*]Ev. Krankenhaus Hattingen GmbH, Klinik für Innere Medizin, Hattingen, Germany; [‡]Gastroenterologická Ambulancia, Poliklinka Druzba, Trnava, Slovak Republic; [§]District Hospital Mladá Boleslav, Mladá Boleslav, Czech Republic; [‖]SOTE II Sz Belgyogyaszati Klinika, Budapest, Hungary; [¶]Gastroenterology Centre of Faculty Hospital IVth, Prague, Czech Republic; [#]Nemocnice Ricany, Interni odd., Říčany, Czech Republic; [**]III Interni Klinika, FNsP ak. Derera, Bratislava, Czech Republic; [‡‡]Hepatogastroenterogie HK s.r.o, Hradec Králové II, Czech Republic; [§§]Orlickoustecka Nemocnice a.s., Usti nad Orlici, Czech Republic; [‖‖]Holy Family Hospital, Nazareth, Israel; [¶¶]Facharztpraxis für Innere Medizin, Berlin, Germany; [##]Department of Gastroenterology, Medical and Health Science Centre, Debrecen, Hungary; [***]Facharztpraxis, Wiesbaden, Germany; [‡‡‡]University Hospital of Heraklion, Heraklion, Crete, Greece; [§§§]Chaim Sheba Medical Center, Tel Hashomer, Israel; [‖‖‖]Department of Gastroenterology, UHC Rijeka, Internal Medicine Clinic, Rijeka, Croatia; [****]Dr Margarete Fischer Bosch Institute of Clinical Pharmacology, Stuttgart and University of Tübingen, Tübingen, Germany; [¶¶¶]medicomp GmbH, Planegg, Germany; and [###]Dr Falk Pharma GmbH, Freiburg, Germany

This article has an accompanying continuing medical education activity on page e13. Learning Objective: Upon completion of this exam, successful learners will be able to identify patients with mild to moderately active Crohn's disease for the treatment with either mesalamine or budesonide.

See related article, Jensen MD et al, on page 124 in *CGH*.

BACKGROUND & AIMS: Comparative data on budesonide vs mesalamine for the treatment of mild-to-moderately active Crohn's disease (CD) are sparse. We assessed the efficacy and safety of each therapy in patients with mildly to moderately active CD. **METHODS:** We performed a randomized, double-blind, double-dummy, 8-week, multicenter study in which 309 patients with mildly to moderately active CD received pH-modified-release oral budesonide (9 mg/day once daily or 3 mg/day 3 times daily) or Eudragit-L–coated oral mesalamine (4.5 g/day). **RESULTS:** The primary efficacy variable, clinical remission (defined as Crohn's Disease Activity Index ≤150), at the final visit occurred in 69.5% (107 of 154) of patients given budesonide vs 62.1% (95 of 153) of patients given mesalamine (difference, 7.4%; 95% repeated confidence interval, −4.6% to 18.0%; $P = .001$ for noninferiority). Clinical remission rates did not differ significantly between the 2 budesonide groups. Treatment response, defined as Crohn's Disease Activity Index of 150 or less and/or a decrease of 70 or more (Δ70) or 100 or more (Δ100) points from baseline to final visit, did not differ significantly between patients given budesonide vs mesalamine (Δ70, $P = .11$; Δ100, $P = .15$), or between the 2 budesonide groups (Δ70, $P = .38$; Δ100, $P = .78$). No other efficacy end points differed significantly between groups. Discontinuation because of adverse events occurred in 3% and 5% of budesonide- and mesalamine-treated patients, respectively. There were no clinically relevant differences in adverse events between the 2 budesonide groups. **CONCLUSIONS: Budesonide (9 mg/day) was numerically, but not statistically, more effective than Eudragit-L–coated mesalamine (4.5 g/day) in patients with mildly to moderately active CD. Budesonide (9 mg/day), administered once daily, was as effective as the standard (3 times daily) regimen.**

Keywords: Mesalamine; Mesalazine; RCT; Remission.

Uncertainty about the etiology of Crohn's disease (CD) means that treatment decisions are made empirically. Selecting the appropriate regimen for an individual patient, however, can be complex because it needs to take into account the activity, localization, and behavior of the disease; the balance between drug potency and adverse events; previous response to treatment; and the presence of extraintestinal manifestations or complications. Recently, guidelines from the European Crohn's and Colitis Organisation[1] recommended that mildly active localized ileocecal CD should be treated with budesonide 9 mg/day based on evidence that it offers superior efficacy to placebo and mesalamine.[2] For moderately ac-

Abbreviations used in this paper: CI, confidence interval; CRP, C-reactive protein; CYP, cytochrome P450; ITT, intent-to-treat; LOCF, last observation carried forward; MDR1, multidrug resistance 1 gene; OD, once daily; PP, per protocol.

0016-5085/$36.00
doi:10.1053/j.gastro.2010.11.004

tive, localized ileocecal disease, the European Crohn's and Colitis Organisation guidelines recommend treatment with either budesonide 9 mg/day or systemic corticosteroids. Budesonide has a superior side-effect profile to conventional steroid therapy[2] because of its relatively low bioavailability,[3] and is better able to preserve adrenal function[2] and bone mass.[4] Superior tolerability might be attributed to extensive first-pass metabolism of budesonide by cytochrome P450 3A (CYP3A) enzymes[5] and to gastrointestinal efflux mediated by P-glycoprotein, a product of the multidrug resistance 1 gene (MDR1).[6] Mesalamine is regarded as showing only limited value in mild-to-moderately active CD on the basis of a meta-analysis of 3 studies conducted in patients with active ileal or colonic CD that concluded that ethylcellulose-coated mesalamine 4 g/day was associated with only a marginal benefit compared with placebo.[7]

However, only a single randomized study published by Thomsen et al[8] a decade ago has directly compared the efficacy and safety of budesonide vs mesalamine for the management of active CD. In that trial, 182 patients with active CD (Crohn's Disease Activity Index [CDAI], 200–400) received either a controlled ileal-release budesonide formulation 9 mg once daily (OD) or 2 g ethylcellulose-coated mesalamine twice daily. After 8 weeks of treatment, clinical remission was observed significantly more frequently with budesonide than mesalamine (69% vs 45%; $P = .001$), a difference that was sustained at week 16 (62% vs 36%; $P < .001$). Since then, no comparative studies of budesonide vs mesalamine have explored the use of alternative formulations to those used in the Thomsen et al[8] study or examined different budesonide dosing regimens.

We report here the findings of a double-blind, double-dummy study in which patients with mildly to moderately active CD were randomized to pH-modified-release budesonide (9 mg/day, given in a single dose or 3 times daily) or Eudragit-L–coated (Evonik, Essen, Germany) oral mesalamine tablets at a dose of 4.5 g/day. The primary objective was to assess the efficacy and safety of each regimen during an 8-week treatment period.

Materials and Methods

Study Design and Conduct

This was a double-blind, double-dummy, randomized, active-controlled, 8-week, phase III study conducted during the period from November 2004 to May 2008 at 46 gastroenterology centers in 7 countries (Croatia, Czech Republic, Germany, Greece, Hungary, Israel, Slovak Republic). In this 3-arm trial, patients were randomized (1:1:2 ratio) to receive budesonide (Budenofalk 3-mg capsules; Dr. Falk Pharma GmbH, Freiburg, Germany) at an oral dose of either 3×3 mg/day or 1×9 mg/day, or oral mesalamine (Salofalk 500-mg tablets; Dr. Falk Pharma GmbH) 3×1.5 g/day. A randomization list was generated by computer using blocks of 4 (RANCODE 3.6; IDV, Gauting, Germany) and was used to dispense study medication to the investigating center according to each patient's unique randomization number. The study was conducted in accordance with the principles of Good Clinical Practice, the Declaration of Helsinki, and all applicable national laws, after approval by independent ethics committees at each of the participating centers. Written informed consent was obtained from all patients. The EudraCT number is 2004-001213-34 (https://eudract.emea.europa.eu/) and the ClinicalTrials.gov identifier is NCT00300118 (http://clinicaltrials.gov/).

Patients

Patients aged 18–70 years were eligible to take part in the study if they had experienced symptoms of CD for at least the preceding 3 months. Diagnosis was to be confirmed by endoscopic and histologic criteria, or by endoscopic and radiologic criteria, with localization of CD in the terminal ileum and/or ascending colon or distal colon. Patients were to be in the active phase of the disease, defined as CDAI score greater than 200 and less than 400. The main exclusion criteria were recognized CD lesions in the upper gastrointestinal tract with current symptoms; CD in the rectum; short-bowel syndrome; abscess, perforation, or active fistulas; ileostomy or colostomy; resection of more than 50 cm of the ileum; clinical signs of stricturing disease; suspected ileus; abnormal renal or hepatic function; treatment with immunosuppressants, cytostatics, methotrexate, or cyclosporine within the past 3 months (in case of treatment with azathioprine or 6-mercaptopurine, the drugs were to have been used only for maintenance of remission and dosage was to be unchanged within the preceding 3 months and during the study); anti–tumor necrosis factor-α therapy within the past 6 months; patients known to be steroid-refractory or steroid-dependent; use of conventional steroid therapy within the preceding 2 weeks; or oral budesonide greater than 6 mg/day or oral mesalamine greater than 3 g/day within the preceding 2 weeks.

Evaluation

Study visits took place at baseline (week 0) and weeks 2, 4, and 6, with a final visit at week 8. Each visit included assessment of CDAI, laboratory parameters, vital signs, adverse events, concomitant therapy, and compliance. Patients were issued with a diary to be completed each day. Compliance was assessed by pill counts and by daily study drug intake as recorded in the patient diaries. CDAI score was calculated retrospectively based on diary entries for the preceding 7 days. Measurement of erythrocyte sedimentation rate and urinalysis was undertaken locally, all other blood analyses were performed centrally. Blood samples for morning serum cortisol level had to be taken between 7:00 and 10:30 AM, and cortisol concentration was evaluated only for patients sampled within this time window. The normal reference range for morning serum cortisol is 5–25 μg/dL.[9]

At the final visit, physicians completed the Physician's Global Assessment questionnaire.

The primary efficacy variable was clinical remission, defined as CDAI of 150 or less, at the week-8 or withdrawal visit. Prespecified subgroup analyses were performed for the primary efficacy variable to assess the consistency of treatment effects across various patient populations. Secondary end points were treatment response, time to clinical remission/treatment response; change in CDAI score, and therapeutic success or therapeutic benefit on the Physician's Global Assessment scale. The time to remission or response was calculated as the interval from baseline to the first recording of a CDAI score of 150 or less, or a decrease of 70 or more (Δ70) or 100 or more (Δ100) points, based on daily diary entries. Safety end points included adverse events (incidence, type, and severity) and laboratory parameters.

At baseline, subjects were genotyped for *MDR1* 3435C>T, and 2677G>T/A.[10] *MDR1* genotypes were stratified according to haplotypes predicting low or high intestinal expression of P-glycoprotein and function.[11] For genetic variants in CYP3A, subjects were genotyped for *CYP3A4*1B* (−392A>G) and for *CYP3A5*3* (intron 3 A>G).[12] *CYP3A5* genotypes were grouped into expressors (*CYP3A5*1/*3*) and nonexpressors (*CYP3A5*3/*3*). All genotypes were in Hardy–Weinberg equilibrium.

Statistics

The primary aim of the study was to show that the rate of clinical remission at the final visit was superior with budesonide (both dose groups combined) vs mesalamine. Based on data in the literature, the sample size calculation assumed that the remission rate would be 55%–60% in budesonide-treated patients and 40%–45% in the mesalamine group (ie, there would be a clinically relevant difference of 15% in the remission rate between treatments). The sample size calculation yielded a total of 368 patients, allowing for drop-outs and an α value of .025 (1-sided).[13] The trial was conducted using a 3-stage adaptive group sequential test design with 2 interim analyses that could lead either to adaptation of the sample size or to cessation of the trial because of successful rejection of the null hypothesis.[14] In addition to the adjusted *P* values, repeated confidence intervals (CIs)[15] (normal approximation) were calculated to allow an estimation of the treatment effect. The option to switch to a noninferiority analysis if the remission rate with mesalamine was considerably higher than expected, in which case there would be a low chance of proving superiority with budesonide therapy, was prespecified in the study protocol. The crucial requirements for the switch from superiority to noninferiority were fulfilled.[16] The trial was properly designed and performed in accordance with the requirements of a noninferiority trial. The noninferiority margin of -10% was predefined in the protocol. This was considered a reasonable margin given an assumed remission rate with placebo and mesalamine of 18%–33%[17,18] and 40%–45%,[18,19] respectively. Statistical significance was demanded for both the intention-to-treat and the per-protocol analysis. Adequate (assay) sensitivity (ie, the ability to detect relevant differences) was ensured by the following requirement in the study protocol: the switch to noninferiority testing was allowed only if superiority of budesonide compared with mesalamine could not be shown on the 2.5% level, although the remission rate with budesonide was at least 55%. This implied that noninferiority testing could be performed only if both active treatments showed remission rates within or above the expected ranges.

The required sample size based on the assumptions described earlier was regarded as adequate based on a noninferiority margin of -0.10, assuming that the remission rate with budesonide would be 5% or higher than with mesalamine. At the first planned interim analysis, involving 220 patients, the Independent Data Monitoring Committee recommended switching the testing of the primary efficacy variable from superiority to noninferiority. By using ADDPLAN (ADDPLAN GmbH, Cologne, Germany)[13] they calculated the sample size required to prove noninferiority with a chance of 80% in the final analysis (overall conditional power) given the remission rates observed at the interim analysis and recommended that an additional 54 patients be enrolled for the second interim analysis and a further 54 patients for the final analysis. The study was still blinded and recruiting. Confirmatory testing of noninferiority was performed using the inverse-normal method of combining the *P* values of the one-sided shifted asymptotic chi-square test for comparing 2 rates and maximum likelihood estimation for the unknown parameters, according to Farrington and Manning.[20]

If a patient discontinued the study prematurely, the last CDAI value recorded with study medication was included (last observation carried forward [LOCF] method). Patients without a postbaseline CDAI value were regarded as not having shown a response to treatment.

All other comparisons were of an exploratory nature. Hence, no correction of *P* values for multiplicity was performed. For subgroup analyses for the primary efficacy variable logistic regression was used. Comparisons of the response rates to treatment were performed using a chi-square test (2-sided) and 95% CIs. The times to remission and to treatment response were compared between groups using a generalized Wilcoxon test and the log-rank test, respectively. For the pharmacogenetic assessment, the results in all patients on budesonide (3 mg 3 times a day or 9 mg OD) were analyzed. Hardy–Weinberg equilibrium was tested using de Finetti program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). Changes in CDAI score and C-reactive protein (CRP) level were compared between different genotypic groups using the 2-sided Wilcoxon 2-sample test.

The safety population comprised all randomized patients who took at least one dose of study medication. The intent-to-treat (ITT) population comprised all patients in the safety population who had active CD at baseline, defined as

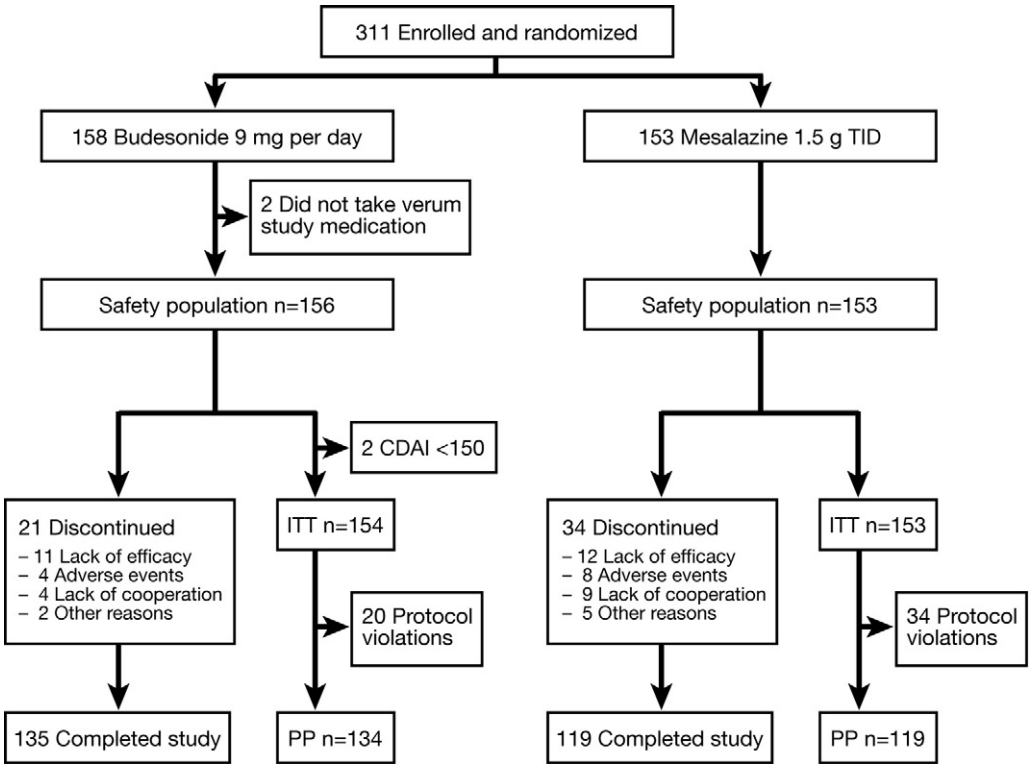

Figure 1. Patient disposition.

CDAI of 150 or greater. The per-protocol (PP) population included all ITT patients without major protocol violations who were adequately compliant (defined as taking >75% of study medication) and provided at least one postbaseline CDAI value with study medication.

Results

Patient Population

In total, 311 patients were recruited (Figure 1). Two patients randomized to budesonide 3 mg, 3 times a day, took no verum study medication and were not evaluable. The remaining 309 patients formed the safety population (79 budesonide 3 mg 3 times a day, 77 budesonide 9 mg OD, and 153 mesalamine). Two patients randomized to budesonide had baseline CDAI of less than 150 and were excluded from the ITT population (78 budesonide 3 mg, 3 times a day, 76 budesonide 9 mg OD, and 153 mesalamine). Twelve patients in the budesonide 3 mg 3 times a day group, 8 patients in the budesonide 9 mg OD group, and 34 patients in the mesalamine group had relevant protocol violations, most frequently use of prohibited concomitant medication and premature discontinuation of the study, such that the PP population included 253 patients (Figure 1). Fifty-five patients discontinued the trial prematurely (12 budesonide 3 mg, 3 times a day; 9 budesonide 9 mg OD, and 34 mesalamine 1.5 g 3 times a day), with 86.5% and 77.8% of budesonide and mesalamine patients completing the study, respectively (Figure 1).

Demographics and baseline characteristics of the treatment groups were rather similar (Table 1). Ten patients received concomitant azathioprine or 6-mercaptopurine (ITT population), with no difference between treatment groups. Overall, 79% (164 of 207) of patients with established disease received at least one treatment for acute episodes in the 2 years before baseline, comprising mesalamine, 69% (142 of 207); conventional steroids, 31% (64 of 207); budesonide, 24% (50 of 207); antibiotics, 16% (33 of 207); azathioprine, 7% (15 of 207); and other treatments, less than 6% (ITT population). Previous treatment was assessed as successful (very good, good, satisfactory) by at least 89% of the patients, and again there was no difference between treatment groups. At least one surgical procedure as a result of CD was reported for 78 patients (25%; ITT population) with the majority (n = 70) undergoing surgery more than 6 months before study entry. There were no meaningful differences in any characteristic between the 2 budesonide dosing groups (data not shown), but mean CDAI was numerically higher in the budesonide OD group at baseline (273 ± 46 vs 259 ± 44 in the 3 times a day cohort), more patients had CDAI greater than 300 (25.0% vs 16.7%), and more patients had extraintestinal manifestations (52.6% vs 42.3%). Medium CRP level (>5 to 10 mg/L) occurred more frequently in the budesonide 9 mg OD group (18.4%) than the 3 mg 3 times a day group (6.4%), but the mean of nontransformed and log-transformed values for CRP level showed no notable differences.

Table 1. Demographics and Baseline Characteristics (ITT Population)

	Budesonide (n = 154)	Mesalamine (n = 153)
Male, n (%)	82 (53.2)	77 (50.3)
White, n (%)	153 (99.4)	152 (99.3)
Age, y		
Mean (SD)	36.8 (12.5)	37.8 (12.5)
Range	18–68	18–68
Age at first diagnosis (Vienna classification), n (%)		109 (71.2)
<40 y	116 (75.3)	44 (28.8)
≥40 y	38 (24.7)	
Body mass index, kg/m^2		
Mean (SD)	23.9 (4.9)	23.8 (4.4)
Range	15.9–39.0	15.6–38.5
Smoking habits, n (%)		
Smoker	47 (30.5)	39 (25.5)
Ex-smoker	15 (9.7)	17 (11.1)
Nonsmoker	92 (59.7)	97 (63.4)
Localization of disease, n (%)		
Terminal ileum and/or ascending colon only	124 (80.5)	133 (86.9)
Distal colon involvement	30 (19.5)	20 (13.1)
Extraintestinal manifestations, n (%)		62 (40.5)
Present	73 (47.4)	91 (59.5)
Not present	81 (52.6)	
Fistula, n (%)		134 (87.6)
Never	134 (87.0)	17 (11.1)
Former	18 (11.7)	1 (0.7)
Current	2 (1.3)	1 (0.7)
Former + current	0 (0.0)	
CDAI at baseline		
Mean (SD)	265.6 (45.4)	267.2 (54.1)
Low (≤300), n (%)	122 (79.2)	114 (74.5)
High (>300), n (%)	32 (20.8)	39 (25.5)
Disease status, n (%)		
New diagnosis	52 (33.8)	48 (31.4)
Established disease	102 (66.2)	105 (68.6)
Duration of disease, y		
Mean (SD)	6.1 (7.0)	5.9 (7.5)
<5, n (%)	89 (57.8)	99 (64.7)
≥5, n (%)	65 (42.2)	54 (35.3)
CRP level at baseline, mg/L		
Mean (SD)	15.4 (20.3)	16.6 (28.5)
≤5, n (%)	75 (48.7)	76 (49.7)
>5 to 10, n (%)	19 (12.3)	23 (15.0)
>10, n (%)	60 (39.0)	54 (35.3)
ESR at baseline		
Mean (SD), mm/first hour	23.3 (20.5)	23.5 (18.3)
≤20 mm/h, n (%)	90 (58.4)	86 (56.2)
>20 mm/h, n (%)	60 (39.0)	61 (39.9)
ESR missing or invalid, n (%)	4 (2.6)	6 (3.9)
AZA/6-MP co-treatment, n (%)		
Yes	5 (3.2)	5 (3.3)
No	149 (96.8)	148 (96.7)
Surgical procedures as a result of CD, n (%)		
At least one surgical procedure	38 (24.7)	40 (26.1)
No surgical procedure	116 (75.3)	113 (73.9)

AZA, azathioprine; ESR, erythrocyte sedimentation rate; 6-MP, 6-mercaptopurine; SD, standard deviation.

Clinical Remission

Clinical remission occurred in 69.5% (107 of 154) of budesonide patients vs 62.1% (95 of 153) of mesalamine patients in the ITT population (difference, 7.4%; 95% repeated CI, −4.6% to 18.0%; $P = .001$ for noninferiority; delta, −10%). The corresponding rates of remission in the PP population were 72.4% (97 of 134) and 68.9% (82 of 119), respectively (difference, 3.5%; 95% repeated CI, −8.7% to 15.5%; $P = .014$ for noninferiority) (Figure 2).

Clinical remission rates in the 2 budesonide dosing groups did not differ significantly: budesonide 3 mg, 3 times a day, 71.8% (56 of 78); budesonide 9 mg OD, 67.1% (51 of 76) (difference, −4.7%; 95% CI, −19.2% to 9.9%; $P = .53$) in the ITT population; 75.8% (50 of 66) and 69.1% (47 of 68) (difference, −6.6%; 95% CI, −21.7% to 8.4%; $P = .39$) in the PP population. This was observed despite the discrepancy in mean CDAI values at baseline, which was mirrored in mean values recorded at the final visit (LOCF) (budesonide 3 mg, 3 times a day, 109 ± 79; budesonide 9 mg OD, 125 ± 92).

Logistic regression analyses regarding the effect of prespecified subgroups and treatment showed a trend to higher remission rates among patients with a low CDAI score (≤300) at baseline (162 of 236 [68.6%]) vs high CDAI score (40 of 71 [56.3%]; $P = .087$), and significantly more frequent remission in patients with a shorter disease duration (132 of 188 [70.2%] for <5 y vs 70 of 119 [58.8%] for ≥5 y; $P = .030$), and among those who did not undergo a surgical procedure for CD (161 of 229 [70.3%] vs 41 of 78 [52.6%] for those undergoing ≥1 procedure; $P = .004$) (ITT population). Women showed a higher clinical response rate with budesonide (75.0% in the ITT population, 77.8% in the PP population) than mesalamine (56.6% and 64.5%, respectively), and the interaction between sex and treatment reached significance on logistic regression analysis in the ITT population ($P = .049$), with a trend to significance in the PP population ($P = .092$). In the subgroup analysis by sex, noninferiority of budesonide was confirmed for women (ITT popula-

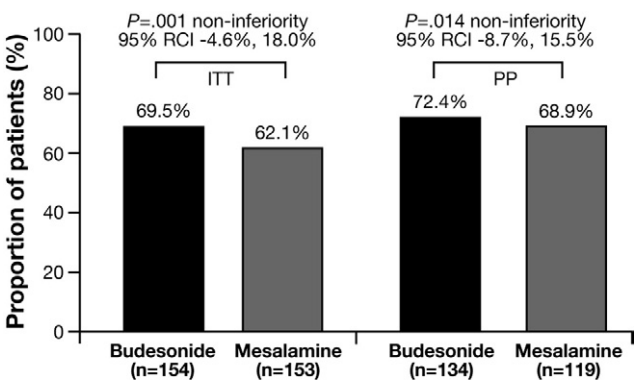

Figure 2. Clinical remission at final study visit, defined as CDAI of 150 or less. RCI, repeated CI.

Table 2. Subgroup Analysis of Clinical Remission Rates According to Characteristics at Baseline

	ITT population		PP population	
	Budesonide	Mesalamine	Budesonide	Mesalamine
Sex				
Male	53/82 (64.6)	52/77 (67.5)	48/71 (67.6)	42/57 (73.7)
Female	**54/72 (75.0)**[a]	**43/76 (56.6)**[a]	49/63 (77.8)	40/62 (64.5)
Extraintestinal manifestations				
Yes	55/73 (75.3)	40/62 (64.5)	50/66 (75.8)	34/50 (68.0)
No	52/81 (64.2)	55/91 (60.4)	47/68 (69.1)	48/69 (69.6)
Localization of inflammation				
Terminal ileum and/or ascending colon only	84/124 (67.7)	85/133 (63.9)	77/108 (71.3)	73/105 (69.5)
Distal colon involvement	23/30 (76.7)[b]	10/20 (50.0)[b]	20/26 (76.9)	9/14 (64.3)
Duration of disease, y				
<5	68/89 (76.4)	64/99 (64.6)	63/79 (79.7)	55/76 (72.4)
≥5	39/65 (60.0)	31/54 (57.4)	34/55 (61.8)	27/43 (62.8)
Surgical procedures for CD				
≥1	19/38 (50.0)	22/40 (55.0)	17/33 (51.5)	18/32 (56.3)
0	88/116 (75.9)	73/113 (64.6)	80/101 (79.2)	64/87 (73.6)
CDAI at baseline				
Low CDAI (≤300)	86/122 (70.5)	76/114 (66.7)	78/105 (74.3)	68/90 (75.6)
High CDAI (>300)	21/32 (65.6)	19/39 (48.7)	19/29 (65.5)	14/29 (48.3)
CRP at baseline, mg/L				
≤5	55/75 (73.3)	54/76 (71.1)	49/65 (75.4)	46/62 (74.2)
>5 to 10	13/19 (68.4)	13/23 (56.5)	12/17 (70.6)	13/20 (65.0)
>10	39/60 (65.0)	28/54 (51.9)	36/52 (69.2)	23/37 (62.2)
ESR at baseline, mm/h[d]				
≤20	59/90 (65.6)	59/86 (68.6)	53/77 (68.8)	49/68 (72.1)
>20	**45/60 (75.0)**[c]	**32/61 (52.5)**[c]	41/54 (75.9)	29/46 (63.0)

NOTE. Data are shown as n (%). Significant differences are shown in bold. Clinical remission was defined as CDAI of 150 or less.
ESR, erythrocyte sedimentation rate.
[a]Difference, 18.4%; 95% CI, 3.5%–33.4%; $P = .0184$.
[b]Difference, 26.7%; 95% CI, 0.03%–53.3%; $P = .0512$.
[c]Difference, 22.5%; 95% CI, 5.9%–39.2%; $P = .0100$.
[d]Ten patients were missing data.

tion, $P < .001$; PP population, $P = .002$), but not for men (ITT population, $P = .171$; PP population, $P = .312$). Of particular note, for patients with a high CDAI score (>300) or high CRP level (>10 mg/L) at baseline, the difference in the rate of clinical remission among budesonide- vs mesalamine-treated individuals was more marked than in patients with a lower level of inflammation and the differences between CDAI and CRP groups approached significance in the ITT population. A comprehensive summary of treatment effects in predefined subpopulations is given in Table 2.

Secondary Efficacy End Points

Treatment response, defined as CDAI of 150 or less and/or a decrease of either 70 or more or 100 or more points from baseline to the final visit, did not differ significantly between budesonide vs mesalamine (Δ70, $P = .11$; Δ100, $P = .15$), or between the 2 budesonide regimens (Δ70, $P = .38$; Δ100, $P = .78$) (Table 3). The median time to remission and treatment response also was similar between groups. The mean CDAI values decreased during the study with both budesonide and mesalamine therapy (Supplementary Figure 1), but the mean reduction from baseline to final visit (LOCF) was approximately 20 points greater in the budesonide groups (150 ± 86 in the budesonide 3 mg 3 times a day group and 148 ± 95 in the budesonide 9 mg OD group compared with 130 ± 108 points in the mesalamine group). The mean CDAI values at baseline and the final visit (LOCF) in the budesonide-treated patients were 266 ± 45 and 117 ± 86, respectively, compared with 267 ± 54 and 137 ± 104 in patients randomized to mesalamine. The difference between the budesonide-treated patients and the mesalamine-treated patients did not reach statistical significance ($P = .094$), whereas the mean change from baseline CDAI was highly statistically significant within all 3 groups.

In terms of individual CDAI items, the number of liquid and very soft stools reduced from baseline to final visit (LOCF) in all treatment groups, but the mean improvement was more marked with budesonide treatment compared with mesalamine (Table 3). Other CDAI item scores showed no marked differences between treatment groups.

Physicians rated treatment as a therapeutic success or a therapeutic benefit numerically, but not significantly, more frequently in the budesonide treatment groups vs mesalamine (Table 3).

Table 3. Secondary Efficacy End Points (ITT Population)

	Budesonide 3 mg 3 times/day	Budesonide 9 mg OD	Budesonide total	Mesalamine 1.5 g 3 times/day
Treatment response (Δ70), n (%)[a]	64/78 (82.1)	58/76 (76.3)	122/154 (79.2)	109/153 (71.2)
Treatment response (Δ100), n (%)[b]	60/78 (76.9)	57/76 (75.0)	117/154 (76.0)	105/153 (68.6)
Median time to clinical remission, days (IQR)	15.0 (7–34)	13.0 (6.5–31.5)	14.0 (7–33)	16.0 (7, right censored)
Median time to treatment response, Δ70, days (IQR)[a]	9.0 (5–18)	6.0 (5–15)	7.0 (5–17)	9.0 (5–29)
Median time to treatment response, Δ100, days (IQR)[b]	14.5 (6–32)	8.0 (6–25)	11.5 (6–30)	13.0 (7–53)
Mean change in CDAI score from baseline to final visit (LOCF) (SD)	−150 (86)	−148 (95)	−149 (91)	−130 (108)
Mean change of number of liquid and very soft stools/wk (SD)	−20.4 (14.6)	−17.9 (18.2)	−19.2 (16.5)	−15.7 (20.0)
Physicians' Global Assessment				
Therapeutic success, n (%)[c]	51/78 (65.4)	45/76 (59.2)	96/154 (62.3)	80/153 (52.3)
Therapeutic benefit, n (%)[d]	69/78 (88.5)	68/76 (89.5)	137/154 (89.0)	121/153 (79.1)

NOTE. All between-group differences were nonsignificant.
[a]Clinical remission (CDAI ≤150) and/or ≥70 decrease in CDAI from baseline to final visit.
[b]Clinical remission (CDAI ≤150) and/or ≥100 decrease in CDAI from baseline to final visit.
[c]Complete relief of symptoms (category 1) or marked improvement of symptoms (category 2).
[d]Complete relief of symptoms (category 1) or marked (category 2), moderate (category 3), or slight (category 4) improvement of symptoms.

Pharmacogenetics of Budesonide

Pharmacogenetic results were available for 89% (119 of 134) of all budesonide-treated patients in the PP population. Allele prevalences suggested that the distribution of this subpopulation was likely to be representative of the general population. The mean decrease in CDAI score or CRP concentration from baseline to the final visit according to *MDR1* haplotypes and *CYP3A4* and *CYP3A5* genotypes is shown in Table 4. None of the comparisons of the decrease in CDAI or CRP between different *MDR1* haplotypes (*MDR1* 3435TT, 2677TT vs *MDR1* 3435CC, 2677GG), between different *CYP3A4*1B* genotypes or between *CYP3A5*3* genotypes showed a statistically significant difference.

Table 4. Decrease in CDAI Score and CRP Concentration From Baseline to Final Visit in Patients Receiving Budesonide 3 mg 3 Times/Day or 9 mg OD (PP Population) According to Different Genotypes

	Decrease in CDAI, points	Decrease in CRP level, mg/L
MDR1 haplotype		
3435TT,2677TT[a] (n = 20)	150 ± 80	1 ± 11
3435CC,2677GG[b] (n = 21)	152 ± 85	8 ± 20
CYP3A4 genotype		
AA (*1/*1, n = 107)	155 ± 83	2 ± 17
AG (*1/*1B, n = 10)	192 ± 68	9 ± 16
CYP3A5 genotype		
GG (*3/*3, nonexpressor, n = 105)	154 ± 82	2 ± 17
AG (*1/*3, expressor, n = 14)	184 ± 73	11 ± 17

NOTE. Data are shown as mean ± SD.
[a]Low intestinal expression of P-glycoprotein.
[b]High intestinal expression of P-glycoprotein.

Safety End Points

Adverse events were reported in 39%, 47%, and 47% of patients in the budesonide 3 mg 3 times a day, budesonide 9 mg OD, and mesalamine groups, respectively. The corresponding incidence of suspected adverse drug reactions was 10%, 12%, and 7%. The majority of adverse events were gastrointestinal, infections, or nervous system disorders (Table 5). Two of 9 serious adverse events (both pancreatitis in the mesalamine group) were assessed as having at least a possible relationship to study drug. Apart from acne (1 patient in the budesonide 9 mg

Table 5. Adverse Events by System Organ Class Occurring in 3% or More of Patients

	Budesonide (N = 156)	Mesalamine (N = 153)
Gastrointestinal disorders	22 (14%)	37 (24%)
Abdominal pain	3 (2%)	8 (5%)
CD	8 (5%)	12 (8%)
Vomiting	3 (2%)	6 (4%)
General disorders and administration site conditions	6 (4%)	6 (4%)
Pyrexia	4 (3%)	5 (3%)
Infections and infestations	25 (16%)	20 (13%)
Viral infection	11 (7%)	5 (3%)
Investigations	10 (6%)	6 (4%)
Blood cortisol decreased[a]	7 (5%)	0 (0%)
Musculoskeletal and connective tissue disorders	7 (5%)	7 (5%)
Back pain	5 (3%)	1 (1%)
Nervous system disorders	17 (11%)	19 (12%)
Headache	14 (9%)	19 (12%)

[a]Spontaneous reporting by investigator; for systematic analysis of morning serum cortisol level see the Results section.

OD group), typical steroid-related adverse drug reactions such as moon face, buffalo hump, hirsutism, and striae were not observed with budesonide treatment. Discontinuation because of adverse events occurred in 3% (n = 4) and 5% (n = 8) of budesonide- and mesalamine-treated patients, respectively.

For patients in whom morning serum cortisol level was measured (budesonide, n = 143; mesalamine, n = 138), the mean ± standard deviation cortisol concentration at baseline was 14.6 ± 7.2 μg/dL in the budesonide-treated patients (budesonide 3 mg 3 times a day, 13.9 ± 6.7 μg/dL; budesonide 9 mg OD, 15.5 ± 7.7 μg/dL) and 15.1 ± 6.6 μg/dL in the mesalamine group. The morning cortisol levels decreased to 9.1 ± 6.8 μg/dL with budesonide at the final visit (LOCF) but remained stable in the mesalamine group (15.9 ± 7.9 μg/dL). This was reflected in the proportion of patients with a shift from normal morning cortisol levels (defined as 5–25 μg/dL) at baseline to a below-normal level at the final visit (LOCF), which occurred in 29% of budesonide patients (31 of 106) and 3% (3 of 107) of mesalamine patients. Remarkably, the proportion of patients with a shift to below-normal morning serum cortisol level was almost identical in both budesonide arms (17 of 55 [31%], budesonide 3 mg 3 times a day; 14 of 51 [27%], budesonide 9 mg OD). In addition, the absolute decrease in morning serum cortisol level did not differ between budesonide 3 mg 3 times a day and 9 mg OD. No notable changes were observed in other laboratory parameters.

Discussion

The results of this double-blind, double-dummy, multicenter trial show that budesonide 9 mg/day (3-mg capsules) is significantly noninferior to mesalamine 4.5 g/day (500-mg tablets) for inducing remission in patients with mildly to moderately active CD within the predefined 10% noninferiority margin. The results indicate that high-dose Eudragit-L–coated mesalamine is associated with a very high rate of remission in mildly to moderately active CD (62% in the ITT population). As anticipated, budesonide 9 mg/day also was found to be highly effective, with approximately 70% of patients achieving remission within 8 weeks. Secondary efficacy end points, including physician assessments, confirmed that there was only a small and nonsignificant difference between the budesonide and mesalamine treatment groups. This unexpected finding contrasts with the results of the only previous randomized trial of budesonide vs mesalamine in this setting.[8]

The high remission rate observed here with budesonide is consistent with European Crohn's and Colitis Organisation recommendations that the preferred treatment for moderately active, localized ileocecal CD is budesonide 9 mg/day or systemic corticosteroids.[1] We observed a particularly high response to budesonide in women, with the difference in clinical remission between the budesonide- and mesalamine-treated patients reaching significance for the women but not for the men. Whether this finding reflects a genuine treatment effect remains uncertain because other studies of budesonide for active CD have observed no sex-specific effect.[8,21,22] A greater numeric advantage for budesonide in terms of clinical remission vs mesalamine was observed in patients with more severe disease, as indicated by high baseline CDAI or increased CRP or erythrocyte sedimentation rate values at baseline. This is compatible with results of the previous randomized trial of budesonide vs mesalamine published by Thomsen et al,[8] which showed a significantly higher response rate for budesonide compared with mesalamine in patients with CDAI greater than 300 (budesonide, 41%; mesalamine, 11%; $P = .001$).

Although tested only in an exploratory sense, these data suggest that once-daily or 3-times-daily administration does not affect the efficacy of budesonide. Interestingly, no efficacy end point differed significantly between the once daily and 3 times daily budesonide regimens. Indeed, the most rapid response was observed in the budesonide 9 mg OD group. Discrepancies in the patient populations at baseline (ie, higher CDAI scores and greater frequency of extraintestinal manifestations in the once-daily cohort) may have contributed to the slightly lower remission rates in the budesonide OD group. The efficacy of oral budesonide 9 mg administered once a day has been shown elsewhere using a different formulation,[17,22] although in previous studies this regimen was only compared with twice-daily dosing and not 3-times-daily dosing, as in the current trial. From a clinical practice perspective, it would seem justified to recommend the budesonide 9 mg OD regimen because this would be expected to improve adherence.

The rate of clinical remission observed in the mesalamine cohort was higher than anticipated based on previous large, controlled studies.[8,18] Interpretation of this finding is not unequivocal because the study did not include a placebo arm owing to ethical considerations, but the following factors tend to indicate that this was a genuine effect of high-dose Eudragit-L–coated mesalamine: the baseline CDAI of 267 in the mesalamine group was compatible with mild to moderate disease activity and was comparable with other placebo-controlled studies.[8,17,23] The mean CDAI decrease of 130 points from baseline to final visit was higher than for placebo in similar patient settings (mean CDAI decrease, 72 points[17] and 45 points[23]), but also much more pronounced than that of ethylcellulose-coated mesalamine.[8,23] Our data suggest that a mesalamine-responsive phenotype of CD exists, characterized by CDAI less than 300 and low CRP level. Although this is in line with the observation that more than a quarter of patients with CD experience a mild long-term course of the disease that requires no treatment except mesalamine,[24] further studies are needed to confirm our assumption. In the previous randomized study of budesonide vs mesalamine for active

CD, the remission rate for mesalamine was 45% compared with the 62% seen here, whereas the remission rate for budesonide (69%) was almost identical to the current study.[8] Certain differences between the trials may account for the different outcomes observed in mesalamine-treated patients. The dose in our trial, at 4.5 g/day, was slightly higher than that used in the former trial (4 g/day). Although most baseline characteristics were similar in the 2 studies, in our trial there were fewer women and patients with previous resections, a shorter duration of disease, and greater previous exposure to mesalamine at study entry. Also, our study used the Eudragit-L–coated formulation of mesalamine (Salofalk), which has a different coating system than the ethylcellulose-coated mesalamine formulation (Pentasa, Ferring, Vanløse, Denmark) administered in the previous study. The 2 galenical formulations result in dissimilar pharmacokinetic profiles: the Eudragit-L–coated formulation releases mesalamine predominantly in the terminal ileum with greater mesalamine absorption, which may be of importance in a transmural condition such as CD.[25]

It is noteworthy that we found no effect of putatively important *CYP3A4* and *CYP3A5* genotypes on the response to oral budesonide. In a clinical pharmacologic trial, intestinal CYP3A4 expression showed an impact on budesonide pharmacokinetics, whereas budesonide pharmacokinetics did not differ between *CYP3A5* genotypic groups.[26] It is well known that a 2677G>T/A single nucleotide polymorphism in exon 21 and a 3435C>T single nucleotide polymorphism in exon 26 of *MDR1* affect expression of P-glycoprotein and thereby the pharmacokinetics of some commonly used drugs.[27] In CD, it has been reported that a poor response to corticosteroids other than budesonide, namely prednisone and hydrocortisone, is related to increased expression of P-glycoprotein.[28] In our study population, however, we observed no hint of a pharmacogenetic effect of MDR1 genetics on the response to oral budesonide therapy.

The overall safety and tolerability of budesonide 9 mg/day was similar to that of mesalamine 4.5 g/day. Both drugs were well tolerated, with approximately 10% of patients experiencing adverse events with at least a possible relation to study drug and a low rate of discontinuations because of adverse events. The difference in incidence of gastrointestinal disorders between the budesonide and mesalamine groups (14% vs 24%, respectively) was owing to exacerbation and symptoms of CD that had to be reported as adverse events, and thus reflected a difference in efficacy rather than in tolerability. As expected from the pharmacodynamic profiles of the study drugs, only budesonide treatment influenced the morning serum cortisol level, with one third of budesonide-treated patients showing a decrease to below the lower limit of normal at the final visit. The observed decrease in cortisol levels is consistent with earlier findings for another oral budesonide formulation given as a regimen of 9 mg OD per day,[29] which induced a markedly less pronounced suppression of pituitary-adrenal function than the conventional steroid prednisolone administered in a tapering schedule from 40 to 5 mg/d over 8 weeks. Overall, the effect of the administration schedule, OD vs 3 times a day, on the suppression of pituitary-adrenal function was similar in our study. There were no marked differences in adverse events or other safety end points between the once-daily and 3-times-daily budesonide groups.

The trial used a robust double-dummy design and the treatment period of 8 weeks has been shown previously to be sufficient for achieving remission in moderately active CD.[21,22,30] The use of the CDAI scale to determine clinical remission is a widely accepted approach and the CDAI-based secondary efficacy end points provided additional sensitivity for detecting a therapeutic response.[31] No placebo arm was included in the trial because this was considered difficult to justify ethically in a population with high disease activity, an approach that was supported by the knowledge that study treatment would achieve remission rates of 40%–60% compared with the 20% remission rate typically seen with placebo.[18,21] Furthermore, the trial was planned under the primary study hypothesis that budesonide would be superior to mesalamine.[8] If this hypothesis had held true, a placebo arm would have been of little extra value. The study protocol was constructed to allow conversion from the planned superiority design to a noninferiority trial, as became necessary owing to the unexpectedly high remission rates with mesalamine, and the sample size was adequate to support the final noninferiority testing.

In conclusion, budesonide 9 mg/day showed numeric, but not statistical, superiority to Eudragit-L–coated mesalamine 4.5 g/day for the treatment of patients with mildly to moderately active CD. In patients with a greater degree of inflammation, there appeared to be a greater benefit for budesonide vs mesalamine, although this did not reach significance. Treatment with either agent was well tolerated, with a low rate of suspected adverse drug reactions or discontinuations owing to intolerance. Interestingly, budesonide 9 mg/day administered OD was as effective and safe as the standard 3-times-daily regimen, which may provide an opportunity to improve treatment compliance.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2010.11.004.

References

1. Dignass A, van Assche G, Lindsay JO, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. J Crohn Colitis 2010;4:28–62.
2. Seow CH, Benchimol EI, Griffiths AM, et al. Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2008;3:CD000296.

3. Edsbäcker S, Jonsson S, Lindberg C, et al. Metabolic pathways of the topical glucocorticoid budesonide in man. Drug Metab Dispos 1983;11:590–596.
4. Schoon EJ, Bollani S, Mills PR, et al. Matrix Study Group. Bone mineral density in relation to efficacy and side effects of budesonide and prednisolone in Crohn's disease. Clin Gastroenterol Hepatol 2005;3:113–121.
5. Jonsson G, Astrom A, Andersson P. Budesonide is metabolized by cytochrome P450 3A (CYP3A) enzymes in human liver. Drug Metab Dispos 1995;23:137–142.
6. Dilger K, Schwab M, Fromm MF. Identification of budesonide and prednisone as substrates of the intestinal drug efflux pump P-glycoprotein. Inflamm Bowel Dis 2004;10:578–583.
7. Feagan BG. Editorial: 5-ASA therapy for active Crohn's disease: old friends, old data and a new conclusion. Clin Gastroenterol Hepatol 2004;2:376–378.
8. Thomsen OO, Cortot A, Jewell D, et al. A comparison of budesonide and mesalamine for active Crohn's disease. N Engl J Med 1998;339:370–374.
9. Murphy BE. Some studies of the protein-binding of steroids and their application to the routine micro and ultramicro measurement of various steroids in body fluids by competitive protein-binding radioassay. J Clin Endocrinol Metab 1967;27:973–990.
10. Meier Y, Pauli-Magnus C, Zanger UM, et al. Interindividual variability of canalicular ATP-binding-cassette (ABC)-transporter expression in human liver. Hepatology 2006;44:62–74.
11. Hoffmeyer S, Burk O, von Richter O, et al. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. Proc Natl Acad Sci U S A 2000; 97:3473–3478.
12. Geisler T, Schaeffeler E, Dippon J, et al. CYP2C19 and nongenetic factors predict poor responsiveness to clopidogrel loading dose after coronary stent implantation. Pharmacogenomics 2008;9:1251–1259.
13. ADDPLAN GmbH. ADDPLAN–adaptive designs, plans and analyses. Release 2.1 and 4.0. Cologne, Germany: 2007.
14. Lehmacher W, Wassmer G. Adaptive sample size calculations in group sequential trials. Biometrics 1999;55:1286–1290.
15. Jennison C, Turnbull BW. Group sequential tests and repeated confidence intervals. In: Ghosh BK, Sen PK, editors. Handbook of sequential analysis. New York: Marcel Dekker, 1991:283–311.
16. EMEA. CPMP/EWP/482/99: points to consider on switching between superiority and non-inferiority. London: EMEA, 2000.
17. Tremaine WJ, Hanauer SB, Katz S, et al. Budesonide CIR capsules (once or twice daily divided-dose) in active Crohn's disease: a randomized placebo-controlled study in the United States. Am J Gastroenterol 2002;97:1748–1754.
18. Singleton JW, Hanauer SB, Gitnick GL, et al. Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. Pentasa Crohn's Disease Study Group. Gastroenterology 1993;104:1293–1301.
19. Tremaine WJ, Schroeder KW, Harrison JM, et al. A randomized, double-blind, placebo-controlled trial of the oral mesalamine (5-ASA) preparation, Asacol, in the treatment of symptomatic Crohn's colitis and ileocolitis. J Clin Gastroenterol 1994;19: 278–282.
20. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med 1990;9: 1447–1454.
21. Greenberg GR, Feagan BG, Martin F, et al. Oral budesonide for active Crohn's disease. Canadian Inflammatory Bowel Disease Study Group. N Engl J Med 1994;331:836–841.
22. Campieri M, Ferguson A, Doe W, et al. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. Gut 1997;41:209–214.
23. Hanauer SB, Strömberg U. Oral Pentasa in the treatment of active Crohn's disease: a meta-analysis of double-blind, placebo-controlled trials. Clin Gastroenterol Hepatol 2004;2:379–388.
24. Bokemeyer B, Katalinic A, Klugmann T, et al. P183–predictive factors for a mild course of Crohn's disease. J Crohn Colitis 2009;3:S82–S83.
25. Tromm A, Griga T, May B. Oral mesalazine for the treatment of Crohn's disease: clinical efficacy with respect to pharmacokinetic properties. Hepatogastroenterology 1999;46:3124–3135.
26. Ufer M, Dilger K, Leschhorn L, et al. Influence of CYP3A4, CYP3A5, and ABCB1 genotype and expression on budesonide pharmacokinetics: a possible role of intestinal CYP3A4 expression. Clin Pharmacol Ther 2008;84:43–46.
27. Marzolini C, Paus E, Buclin T, et al. Polymorphisms in human MDR1 (P-glycoprotein): recent advances and clinical relevance. Clin Pharmacol Ther 2004;75:13–33.
28. Farrell RJ, Murphy A, Long A, et al. High multidrug resistance (P-glycoprotein 170) expression in inflammatory bowel disease patients who fail medical therapy. Gastroenterology 2000;118: 279–288.
29. Rutgeerts P, Lofberg R, Malchow H, et al. A comparison of budesonide with prednisolone for active Crohn's disease. N Engl J Med 1994;331:842–845.
30. Gross V, Andus T, Caesar I, et al. Oral pH-modified release budesonide versus 6-methylprednisolone in active Crohn's disease. German/Austrian Budesonide Study Group. Eur J Gastroenterol Hepatol 1996;8:905–909.
31. Thia KT, Sandborn WJ, Lewis JD, et al. Defining the optimal response criteria for the Crohn's disease activity index for induction studies in patients with mildly to moderately active Crohn's disease. Am J Gastroenterol 2008;103:3123–3131.

Received March 24, 2010. Accepted November 3, 2010.

Reprint requests

Address requests for reprints to: Professor Andreas Tromm, MD, Ev. Krankenhaus Hattingen GmbH, Klinik für Innere Medizin, Bredenscheider Str. 54, 45525 Hattingen, Germany. e-mail: a.tromm@krankenhaus-hattingen.de; fax: (49) 2324-502-366.

Acknowledgments

The authors give special thanks to P. Heine and R. Schwarz (medicomp GmbH, Planegg, Germany) for their assistance in conducting the clinical trial. The authors would like to thank all patients and investigators for their participation and contribution to the study.

Editorial assistance, comprising revision and finalization of the draft manuscript prepared by the authors, was provided by freelance writer Caroline Dunstall, with funding from Dr. Falk Pharma GmbH.

Conflicts of interest

The authors disclose the following: Andreas Tromm has received speaker's honoraria and travel funding from Dr Falk Pharma GmbH; Karin Dilger, Ralf Mohrbacher, and Roland Greinwald are employees of Dr Falk Pharma GmbH. The remaining authors disclose no conflicts.

Funding

The study was funded by Dr. Falk Pharma GmbH, Freiburg, Germany. The study sponsor contributed to the design of the study in collaboration with the authors, funded the analysis of the data by an independent biostatistics company, and worked in conjunction with the authors to interpret the data. The sponsor was not involved in data collection. ES was supported by the Robert-Bosch Foundation, Stuttgart, Germany and from the Federal Ministry for Education and Research (BMBF, Berlin, Germany; 03 IS 2061C).

Appendix

The International Budenofalk Study Group was as follows: Croatia: Dr Mate Kozic (Zadar), Professor Milan Kujundzic (Zagreb), Professor Stjepan Miše (Split), Professor Davor Štimac (Rijeka), Professor Aleksandar Včev (Osijek); Czech Republic: Professor Bohumil Fixa (Hradec Králové), Dr Josef Doseděl (Prague), Dr Ladislav Douda (Tabor), Dr Libor Gabalec (Usti nad Orlici), Dr Michal Konečný (Olomouc), Dr Jan Kykal (Řičany), Dr Jiří Laštùvka (Usti nad Labem), Professor Milan Lukáš (Prague), Dr Eva Tomsová (Mladá Boleslav), Dr Ondřej Urban (Ostrava-Vítkovice), Dr Dana Voharciková (Teplice), Dr Vladimir Zbořil (Brno); Germany: Dr Dietrich Hüppe (Herne), Dr Andreas Kocjan (Lüdenscheid), Dr Heinz-Jochen Kramm (Berlin), Professor Hanns Löhr (Wiesbaden), Professor Stephan Miehlke (Dresden), Dr Moritz Müser (Lüdenscheid), Professor Stefan Zeuzem (Homburg); Greece: Dr Ioannis Koutroubakis (Heraklion, Crete), Dr Gerassimos J. Mantzaris (Athens); Hungary: Professor István Altorjay (Debrecen), Professor Zoltan Döbrönte (Szombathely), Dr Zsolt Dubravcsik (Kecskemét), Professor István Rácz (Györ), Professor Zsolt Tulassay (Budapest), Dr László Újszászy (Miskolc); Israel: Professor Simon-Bar Meir (Tel Hashomer), Dr Iris Dotan (Tel Aviv), Dr Mark Faszczyk (Ashkelon), Professor Zvi Fireman (Hadera), Professor Fred Konikoff (Kfar Saba), Dr Ehud Melzer (Rechovot), Professor Yaron Niv (Petach Tikva), Dr Rifaat Safadi (Nazareth), Professor Eitan Scapa (Zrifin); Slovak Republic: Dr Boris Barický (Nitra), Professor Marian Bátovský (Bratislava), Dr Ivan Bunganič (Presov), Dr Igor Katancík (Presov), Dr Božena Pekárková (Trnava).

Members of the independent data monitoring committee were as follows: Martin Krauss (statistician), Professor Tilo Andus (gastroenterologist), and Professor Gerhard Rogler (gastroenterologist).

Supplementary Figure S1. Mean CDAI during the study (ITT population).