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Budesonide Foam Induces Remission in Patients With Mild to Moderate Ulcerative Proctitis and Ulcerative Proctosigmoiditis

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BACKGROUND & AIMS: Budesonide is a high-potency, second-generation corticosteroid designed to minimize systemic adverse consequences of conventional corticosteroids. We performed 2 randomized, phase 3 trials to evaluate the ability of budesonide rectal foam, formulated to optimize retention and provide uniform delivery of budesonide to the rectum and distal colon, to induce remission in patients with ulcerative proctitis or ulcerative proctosigmoiditis. **METHODS:** Two identically designed, randomized, double-blind, placebo-controlled trials evaluated the efficacy of budesonide foam for induction of remission in 546 patients with mild to moderate ulcerative proctitis or ulcerative proctosigmoiditis who received budesonide foam 2 mg/25 mL twice daily for 2 weeks, then once daily for 4 weeks, or placebo. **RESULTS:** Remission at week 6 occurred significantly more frequently among patients receiving budesonide foam than placebo (Study 1: 38.3% vs 25.8%; $P = .0324$; Study 2: 44.0% vs 22.4%; $P < .0001$). A significantly greater percentage of patients receiving budesonide foam vs placebo achieved rectal bleeding resolution (Study 1: 46.6% vs 28.0%; $P = .0022$; Study 2: 50.0% vs 28.6%; $P = .0002$) and endoscopic improvement (Study 1: 55.6% vs 43.2%; $P = .0486$; Study 2: 56.0% vs 36.7%; $P = .0013$) at week 6. Most adverse events occurred at similar frequencies between groups, although events related to changes in cortisol values were reported more frequently with budesonide foam. There were no cases of clinically symptomatic adrenal insufficiency. **CONCLUSIONS:** Budesonide rectal foam was well tolerated and more efficacious than placebo in inducing remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis. ClinicalTrials.gov ID: NCT01008410 and NCT01008423.

Keywords: Inflammatory Bowel Disease; Ulcerative Colitis; Budesonide; Ulcerative Proctosigmoiditis.

Ulcerative proctitis (UP) and ulcerative proctosigmoiditis (UPS) are part of the spectrum of ulcerative colitis (UC), an idiopathic chronic inflammatory disease of the colon that is believed to be immune-mediated.[1] Approximately 46% of patients with UC are diagnosed with UP or UPS.[2,3] Clinical UC symptoms include rectal bleeding, diarrhea, urgency, tenesmus, and abdominal pain.[1] Oral or rectal mesalamine is often administered as first-line therapy.[4,5] Suppositories and liquid enemas are recommended for the induction of remission in patients with mild to moderate UP, and they can be administered alone or in combination with oral mesalamine when mild to moderate disease extends beyond the rectum.[1,6,7] However, these rectal therapies have several limitations, including difficulty of administration, retention, and limited proximal spread. For example, suppositories disperse no further than the rectum, and while liquid enemas can spread to the splenic flexure, they are difficult for patients to retain and require patients to remain recumbent for a specified period of time after administration.[1,8,9]

Although active UP and UPS can be treated effectively with systemic corticosteroids,[6,10–12] their use can result in adverse effects, including mood and sleep changes, Cushingoid appearance, weight gain, fluid retention, acne, and hirsutism; longer-term use of systemic steroids can lead to more serious adverse effects, such as increased risk of infections, decreased bone density, ocular complications (eg, glaucoma, cataracts), and adrenal insufficiency.[6,13] There remains an unmet need for therapies that can target the area of active inflammation and yet have fewer systemic effects than conventional steroids.

High-potency, second-generation corticosteroids, including budesonide and beclomethasone, can be administered either rectally or orally to produce a topical anti-inflammatory effect. Budesonide has nearly 90% first-pass hepatic metabolism, thus reducing the potential for corticosteroid-related adverse events (AEs).[13–15] A randomized, double-blind, dose-ranging study of patients with active UP or distal UC receiving budesonide enema demonstrated efficacy (ie, increased rate of remission vs placebo, improved endoscopic inflammation and histology scores

Abbreviations used in this paper: **ACTH, adrenocorticotropic hormone; AE, adverse event; UC, ulcerative colitis; UP, ulcerative proctitis; UPS, ulcerative proctosigmoiditis.**

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relative to baseline) for up to 6 weeks.[16] In an active comparator study of patients with active UP, UPS, or left-sided UC, budesonide enema had a safety profile similar to that of mesalamine enema, although mesalamine enema induced remission in a significantly greater percentage of patients compared with budesonide enema (77.2% vs 63.5%, respectively; $P < .05$).[17] Beclomethasone foam and enema were shown to have efficacy and safety profiles similar to those observed for mesalamine foam and enema in patients with mild to moderate UP or UPS after 8 weeks.[18]

Budesonide foam is a new rectal formulation of budesonide that optimizes drug retention and provides uniform drug delivery to the rectum and distal colon, with a maximal spread of up to 40 cm (mean, 25.4 cm).[19] Budesonide foam had an efficacy profile comparable with that of hydrocortisone foam for treatment of UP and UPS, with no significant impact on cortisol concentrations or increased occurrence of corticosteroid-related AEs when administered for up to 8 weeks.[20] A majority of patients with active UP or UPS preferred a steroid foam formulation to a steroid enema formulation.[21] To evaluate the efficacy and safety of budesonide foam relative to placebo in patients with active, mild to moderate UP and UPS, we conducted 2 identically designed, 6-week, double-blind induction trials.

Methods

Patients

Patients aged 18 years and older with active UP or UPS extending at least 5 cm, but no further than 40 cm from the anal verge, were eligible for enrollment. Patients had mild to moderate disease, with a baseline Modified Mayo Disease Activity Index score (hereafter referred to as "Mayo score") between 5 and 10, inclusive, with subscale ratings of $\geq$2 for endoscopic appearance and rectal bleeding. The Mayo score is the sum of 4 subscale scores: stool frequency, rectal bleeding, endoscopic findings, and a physician's global assessment. Since publication of the original Mayo Disease Activity Index,[22] the endoscopy subscale was modified such that patients with any degree of friability are classified as having a subscale score of 2.

Exclusion criteria included evidence of Crohn's disease or indeterminate colitis, significant comorbid condition, a positive stool test for bacterial pathogens (*Clostridium difficile* toxin, or ovum and parasites), and adrenal insufficiency, defined as a measurement of $<$18 μg/dL serum cortisol after adrenocorticotropic hormone (ACTH) challenge. Medication restrictions included use of systemic, oral, topical, or rectal corticosteroids; laxatives; enemas; treatments for irritable bowel syndrome (eg, alosetron, lubiprostone); anticoagulants; rectal mesalamine therapies; oral mesalamine therapies at dosages of $>$4.8 g/d; narcotics; antibiotics; and antidiarrheal medications (eg, loperamide, bismuth subsalicylate).

The protocol was approved by institutional review boards and ethics committees. All patients provided written informed consent. All authors had full access to the study data and reviewed and approved the final manuscript.

Study Design

Two identically designed, phase 3, randomized, double-blind, placebo-controlled, multicenter studies (Study 1 [ClinicalTrials.gov ID: NCT01008410] and Study 2 [ClinicalTrials.gov ID: NCT01008423]) were conducted in the United States and Russia during November 2009 to March 2013 (Study 2) or to April 2013 (Study 1). Patients were assigned to a treatment group via a randomization schedule, stratified by study center, generated by an interactive voice response system/interactive web response system. Patients were randomized in a 1:1 allocation to receive budesonide rectal foam 2 mg/25 mL or placebo twice daily for 2 weeks, then once daily for 4 weeks. Concomitant use of oral mesalamine drugs at a stable dosage of up to 4.8 g/d was permitted. Each study consisted of a screening phase (completed within 7 days of randomization), a single-blind run-in/stabilization phase of 4 to 7 days, a 6-week double-blind treatment phase, and a 2-week follow-up phase (Supplementary Figure 1). Via administration of a placebo, the single-blind run-in/stabilization phase allowed patients to practice and familiarize themselves with appropriate use of the foam delivery device before the treatment phase of the study. Patients were required to meet inclusion criteria after the run-in/stabilization phase to continue in the study. A colonoscopy was required for patients newly diagnosed or without a confirmed diagnosis of UC within 12 months of the screening visit. Colonoscopy, if needed, was performed no more than 10 days, and no less than 4 days, before randomization. If a colonoscopy was not required, patients were scheduled for sigmoidoscopy 4 to 7 days before randomization. Histology results from the colonoscopy were required from patients with newly diagnosed UC, before randomization, to confirm active UP or UPS.

Assessments

The primary efficacy end point was the percentage of patients achieving remission at week 6 (defined as an endoscopy subscore $\leq$1, rectal bleeding subscore of 0, and improvement or no change from baseline in the stool frequency subscore of the Mayo score). Scores ranged from 0 to 3 for each subscore of the Mayo score (endoscopy subscore: 0 = normal or inactive disease, 1 = mild disease, 2 = moderate disease, 3 = severe disease; rectal bleeding subscore: 0 = no blood seen, 1 = streaks of blood with stool less than half the time, 2 = obvious blood with stool most of the time, 3 = blood alone passed; stool frequency subscore: 0 = normal number of stools per day for each individual patient, 1 = 1 to 2 stools more than normal, 2 = 3 to 4 stools more than normal, 3 = $\geq$5 stools more than normal; physician's global assessment subscore: 0 = normal, 1 = mild disease, 2 = moderate disease, 3 = severe disease). Endoscopic disease extent and activity were determined by local investigators.

Key secondary efficacy end points included the percentage of patients achieving a Mayo rectal bleeding subscore of 0 at week 6, the number of scheduled assessments (weeks 1, 2, 4, and 6) in which patients had a rectal bleeding subscore of 0, and the percentage of patients achieving a Mayo endoscopy subscore of 0 or 1 at week 6. Safety assessments included monitoring of AEs, clinical laboratory tests (including morning cortisol concentrations and ACTH challenge tests), and vital signs. For purposes of reporting

laboratory-derived AEs, adrenal insufficiency was defined as having a serum cortisol of ≤18 μg/dL at 30 minutes post-ACTH challenge.

Pharmacokinetic Analysis

Blood samples for budesonide pharmacokinetic assessments were collected on multiple visits from patients in the United States. The time of administration of the most recent dose of study drug and the time of blood collection were recorded. Plasma budesonide concentrations were determined using a validated high-performance liquid chromatography/dual mass spectrometry method. Plasma budesonide concentrations were summarized by descriptive statistics and analyzed by population-based pharmacokinetic methods using NONMEM version 7.2 (ICON plc, Hanover, MD). Statistical comparisons of pharmacokinetic data were performed using the extended rank-sum test.[23]

Statistical Analyses

All patients randomized to treatment were included in the intention-to-treat population. The safety population included patients in the intention-to-treat population who received ≥1 dose of the study drug. Baseline characteristics, clinical laboratory values, and AEs were summarized descriptively. Differences in treatment arms for the primary efficacy end point and secondary efficacy end points with percentages as outcomes were analyzed using a logistic regression model after adjusting for analysis center effect. Subgroup analyses of the primary end point were conducted based on the data combined from the 2 studies, by the same method that was used to analyze the primary end point. Secondary efficacy outcomes with categorized changes (eg, change from baseline in Mayo score) were analyzed using an ordinal logistic regression test, adjusting for analysis center effect. Analysis of change from baseline was performed by fitting fixed effects linear models to the data. Analyses of ordinal data (eg, the number of scheduled assessments with rectal bleeding responder classifications) were performed using the proportional odds model for ordinal outcome (ie, PROC LOGISTIC in SAS/STAT 9.3 software; SAS Institute Inc, Cary, NC), adjusting for country effect. Multiplicity of the key secondary efficacy outcomes was addressed by statistical testing of the end points in a hierarchical manner: the percentage of patients achieving a Mayo rectal bleeding subscore of 0 at week 6, the number of scheduled assessments (weeks 1, 2, 4, and 6) in which patients had a rectal bleeding subscore of 0, and 3), and the percentage of patients achieving a Mayo endoscopy subscore of 0 or 1 at week 6. Mean compliance percentages were calculated using the following equation:

$$\%\ \text{compliance} = \frac{(100 * [\text{no. of applicators dispensed} - \text{no. of applicators returned}])}{(\text{no. of applicators scheduled for use per planned treatment regimen})}$$

Sample size estimates assumed remission rates of 40% and 23% for budesonide foam and placebo, respectively, for both studies. Based on the assumed remission rates and a significance level of $\alpha = .05$, it was determined that 133 patients were needed in each treatment arm for each study to test the primary efficacy end point with a power of 85%.

Results

Patient Disposition and Demographics

A total of 546 patients (budesonide foam, n = 267; placebo, n = 279) were included in the intention-to-treat population of the 2 studies (Supplementary Figure 2). In Study 1, one patient was randomized to treatment with placebo but received both placebo and budesonide foam during the study; this patient was included in the placebo group for all efficacy analyses and in the budesonide foam group for all safety analyses as prespecified in the statistical analysis plan. In Study 2, one patient randomized to treatment with budesonide foam received placebo and was included in the budesonide foam group for all efficacy and safety analyses as prespecified in the statistical analysis plan. The majority of patients in each treatment arm (>80%) completed the studies.

Demographic and baseline characteristics were generally comparable across treatment groups for each study (Table 1). Most (approximately 90%) patients in each treatment group were white, >50% were female, and the mean ages across groups were 41 to 44 years. At baseline, the mean total Mayo score was 8 for patients in each treatment group, and the mean number of daily normal stools ranged between 1.3 and 1.4. At least 67% of patients in each treatment arm of both studies had proctosigmoiditis (disease extending up to approximately 40 cm from the anal verge), and approximately 26% to 33% of patients had proctitis (disease extending approximately 15 cm from the anal verge). More than half of patients receiving budesonide foam or placebo in the studies reported concomitant use of mesalamine or related compounds at baseline.

Most (>80%) patients were exposed to study drug for 29 to 44 days, with a mean duration of 38.8 (SD, 9.9) days and 39.1 (SD, 9.2) days, for budesonide foam and placebo, respectively, for the combined studies. Overall compliance was high and was comparable between the 2 treatment groups overall (budesonide foam, 94.0% vs placebo, 97.1%), during twice-daily dosing (through week 2; 94.4% vs 97.0%, respectively) and once-daily dosing (week 3 to week 6; 94.3% vs 97.5%, respectively).

Efficacy

Remission at week 6 (primary efficacy end point) was achieved in a significantly greater percentage of patients receiving budesonide foam compared with placebo in Study 1 and Study 2 (Figure 1). A significantly greater percentage of patients treated with budesonide foam achieved the key secondary outcome of a rectal bleeding subscore of 0 at week 6 compared with placebo in both Study 1 ($P = .0022$) and Study 2 ($P = .0002$; Figure 2*A*). The number of scheduled assessments (out of 4) in which patients had a rectal bleeding subscore of 0 significantly favored treatment with budesonide foam (Study 1: $P = .0004$; Study 2: $P < .0001$). In Study 1, a greater percentage of patients receiving budesonide foam compared with placebo achieved rectal bleeding subscores of 0 at 2 (18.8% vs 13.6%, respectively), 3 (21.1% vs 10.6%), and 4 (6.0% vs 1.5%) assessments. In

Table 1. Demographic and Baseline Characteristics (Intention-to-Treat Population)

Parameter	Study 1[a]		Study 2[b]	
	Budesonide foam 2 mg/25 mL (n = 133)	Placebo (n = 132)	Budesonide foam 2 mg/25 mL (n = 134)	Placebo (n = 147)
Age, *y*, mean (SD)	43.2 (13.9)	41.4 (13.2)	44.3 (13.5)	41.9 (13.3)
Sex, n (%)				
Male	61 (45.9)	52 (39.4)	62 (46.3)	63 (42.9)
Female	72 (54.1)	80 (60.6)	72 (53.7)	84 (57.1)
Race, n (%)				
White	115 (86.5)	123 (93.2)	119 (88.8)	135 (91.8)
Other	18 (13.5)	9 (6.8)	15 (11.2)	12 (8.2)
BMI, kg/m^2, mean (SD)	26.7 (5.8)	26.8 (5.5)	25.7 (5.3)	25.4 (4.7)
Duration of disease, *y*, mean (SD)	4.5 (6.9)	5.0 (7.0)	5.4 (6.3)	3.8 (4.8)
Extent of disease, n (%)				
Proctitis[c]	37 (27.8)	43 (32.6)	35 (26.1)	38 (25.9)
Proctosigmoiditis[d]	95 (71.4)	88 (66.7)	98 (73.1)	109 (74.1)
Missing	1 (0.8)	1 (0.8)	1 (0.7)	0
Baseline extent of disease, *cm*, mean (SD)	23.8 (10.2)	22.3 (10.0)	25.2 (10.9)	25.0 (10.1)
Baseline Mayo total score, mean (SD)	7.8 (1.2)	7.9 (1.3)	7.9 (1.3)	8.0 (1.2)
Severity of disease, n (%)				
Mild (Mayo score 4–6)	15 (11.3)	22 (16.7)	13 (9.7)	12 (8.2)
Moderate (Mayo score 7–10)	118 (88.7)	110 (83.3)	119 (88.8)	135 (91.8)
Severe (Mayo score 11–12)	0	0	2 (1.5)	0
Baseline Mayo rectal bleeding subscore, n (%)				
0	1 (0.8)	0	0	0
1	1 (0.8)	2 (1.5)	3 (2.2)	1 (0.7)
2	116 (87.2)	113 (85.6)	112 (83.6)	123 (83.7)
3	15 (11.3)	17 (12.9)	19 (14.2)	23 (15.6)
Baseline Mayo endoscopy subscore, n (%)				
Normal or inactive	0	0	0	0
Mild	0	0	0	0
Moderate	120 (90.2)	120 (90.9)	117 (87.3)	134 (91.2)
Severe	13 (9.8)	12 (9.1)	17 (12.7)	13 (8.8)
Baseline Mayo bowel frequency subscore, n (%)				
0	9 (6.8)	10 (7.6)	13 (9.7)	9 (6.1)
1	37 (27.8)	35 (26.5)	44 (32.8)	49 (33.3)
2	56 (42.1)	47 (35.6)	44 (32.8)	53 (36.1)
3	31 (23.3)	40 (30.3)	33 (24.6)	36 (24.5)
Baseline Mayo physician global assessment subscore, n (%)				
0	0	0	0	0
1	25 (18.8)	23 (17.4)	7 (5.2)	10 (6.8)
2	105 (78.9)	107 (81.1)	125 (93.3)	133 (90.5)
3	3 (2.3)	2 (1.5)	2 (1.5)	4 (2.7)
Normal no. of stools/d, mean (SD)	1.3 (0.6)	1.4 (0.7)	1.4 (0.8)	1.4 (0.6)
Baseline use of mesalamine, n (%)	78 (58.6)	79 (59.8)	69 (51.5)	75 (51.0)
Baseline use of corticosteroids, n (%)	1 (0.8)	0	1 (0.7)	0
Baseline use of immunosuppressants, n (%)	1 (0.8)	0	0	0
Baseline use of biologics, n (%)	0	0	0	0

BMI, body mass index.
[a]One patient was randomized to treatment with placebo but received both placebo and budesonide foam during the study. This patient was included in the placebo group for the efficacy analyses and the budesonide foam group for the safety population analyses.
[b]One patient was randomized to treatment with budesonide foam but received placebo during the study; this patient is included in the budesonide foam group for efficacy and safety analyses.
[c]Proctitis was defined as disease limited to the rectum (up to approximately 15 cm).
[d]Proctosigmoiditis was defined as disease limited to the rectum and sigmoid colon (up to approximately 40 cm from the anal verge).

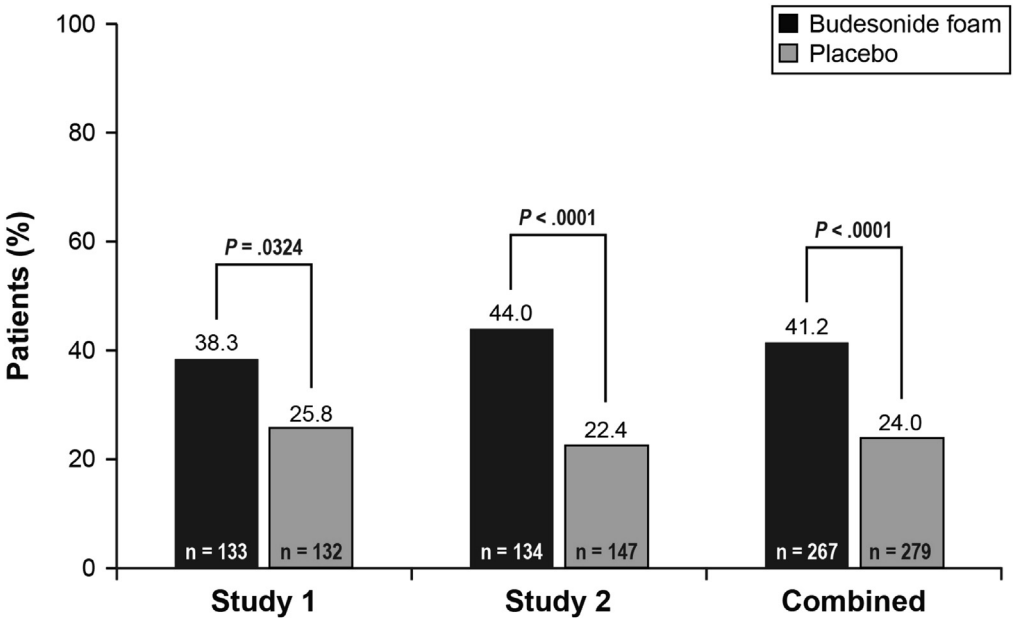

Figure 1. Patients achieving remission at week 6 (primary efficacy measure). Remission defined as endoscopy score ≤ 1, rectal bleeding score $= 0$, and improvement or no change from baseline in stool frequency subscales of the Mayo score.

Study 2, achievement of rectal bleeding subscores of 0 occurred in a greater percentage of patients receiving budesonide foam compared with placebo at 3 assessments (21.6% vs 7.5%, respectively) and 4 assessments (13.4% vs 2.0%).

A rectal bleeding subscore of 0 was achieved within 1 week in a significantly greater percentage of patients receiving budesonide foam compared with placebo (Study 1: $P = .0438$; Study 2: $P = .0043$). The percentage of patients with a rectal bleeding response to budesonide foam vs placebo increased by the second week of twice-daily dosing, continued to improve at week 4 (once-daily dosing), and was maintained at week 6 (once-daily dosing; Figure 2*B*) in both studies. In addition, a significantly greater percentage of patients receiving budesonide foam compared with placebo achieved an endoscopy subscore of 0 or 1 at week 6 in both Study 1 ($P = .0486$) and Study 2 ($P = .0013$; Figure 2*C*). A greater percentage of patients in the budesonide foam group achieved improvement or no change from baseline in the Mayo stool frequency score compared with the placebo group in Study 1 (78.9% vs 68.9%, respectively; $P = .07$) and in Study 2 (79.9% vs 72.8%, respectively; $P = .18$), although these differences were not significant. When expressed according to the percentage of patients with improvement from baseline in the Mayo stool frequency score, rates for budesonide foam were numerically greater than those for placebo at weeks 1, 2, 4, and 6 in both Study 1 (week 1, 49.6% vs 36.4%, respectively; week 2, 57.1% vs 40.2%; week 4, 54.9% vs 43.9%; and week 6, 52.6% vs 41.7%) and Study 2 (week 1, 41.0% vs 34.7%, respectively; week 2, 52.2% vs 45.6%; week 4, 56.7% vs 46.9%; and week 6, 53.0% vs 42.2%).

In the combined population, the primary efficacy end point of remission was achieved by a significantly greater percentage of patients receiving budesonide foam compared with placebo ($P < .0001$; Figure 1). A significantly greater percentage of patients treated with budesonide foam achieved a rectal bleeding subscore of 0 at week 6 compared with placebo in the combined population ($P < .0001$; Figure 2*A*). The number of scheduled assessments (out of 4) in which patients had a rectal bleeding subscore of 0 significantly favored treatment with budesonide ($P < .0001$). A rectal bleeding subscore of 0 was achieved within 1 week in a significantly greater percentage of patients in the combined population receiving budesonide foam compared with placebo ($P = .0005$; Figure 2*B*). A significantly greater percentage of patients receiving budesonide foam compared with placebo achieved an endoscopy subscore of 0 or 1 at week 6 in the combined studies ($P = .0002$; Figure 2*C*).

When the primary end point was examined according to relevant demographic and baseline characteristics, budesonide foam was superior to placebo for nearly all subgroups examined (ie, age, sex, white race, mild or moderate disease severity, established disease, smoking history, extent of disease, baseline use of mesalamine, and country; Supplementary Figure 3). For example, budesonide foam was more efficacious than placebo in patients with UP (treatment difference = 14.6%; $P = .0315$), as well as in those with UPS (treatment difference = 18.2%; $P = .0002$). Similarly, the treatment effect for patients in the United States (treatment difference = 15.6%; $P = .0005$) and Russia (treatment difference = 18.2%; $P = .008$) favored budesonide foam over placebo. Subgroups for which statistical significance vs placebo was not achieved tended to have a low number of patients (ie, nonwhite race, mild disease severity, and newly diagnosed disease).

Safety

The majority of AEs associated with treatment with budesonide foam were mild to moderate in intensity (Table 2). The most common AEs reported during treatment

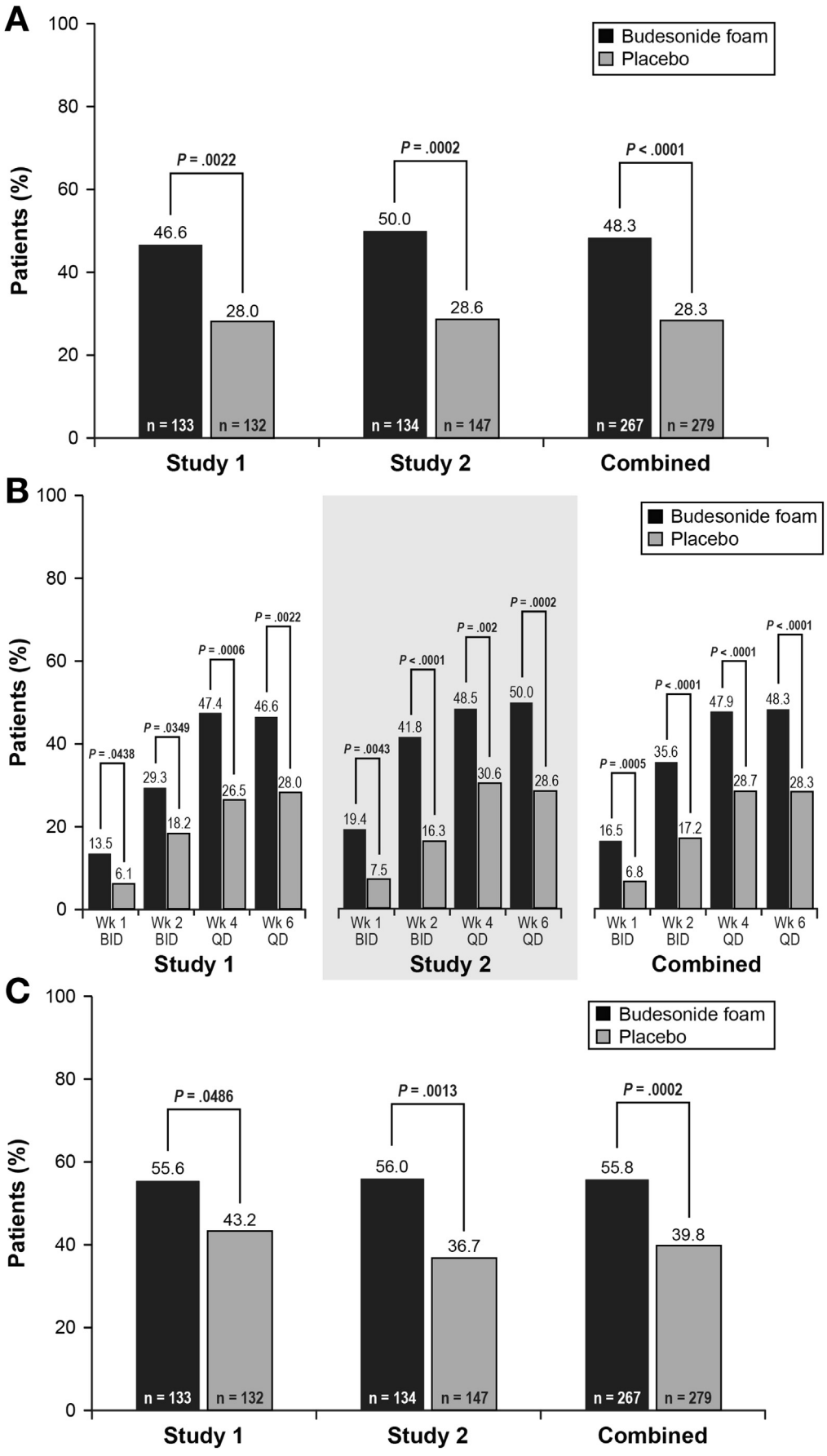

Figure 2. Patients achieving secondary efficacy outcome measures. (*A*) Mayo rectal bleeding subscore = 0 at week 6. (*B*) Week in which patients received a Mayo rectal bleeding subscore = 0. (*C*) Mayo endoscopy subscore $\leq$1 at week 6. BID, twice daily; QD, once daily.

Table 2. Summary of Adverse Events (Combined Analysis)

Adverse event	Budesonide foam 2 mg/25 mL (n = 268)[a]	Placebo (n = 278)
Any AE, n (%)	123 (45.9)	101 (36.3)
Discontinuation due to AE	26 (9.7)	12 (4.3)
Serious AEs	5 (1.9)	3 (1.1)
Intensity of AE, n (%)[b,c]		
Mild	88 (32.8)	57 (20.5)
Moderate	27 (10.1)	40 (14.4)
Severe	8 (3.0)	4 (1.4)
Most common AEs, n (%)[d]		
Decreased blood cortisol concentrations	46 (17.2)	6 (2.2)
Adrenal insufficiency	10 (3.7)	2 (0.7)
Headache	6 (2.2)	7 (2.5)
Nausea	6 (2.2)	2 (0.7)
Ulcerative proctitis	0	6 (2.2)

[a]One patient in Study 1 was randomized to treatment with placebo but received both placebo and budesonide foam during the study. This patient was included in the placebo group for the efficacy analyses and the budesonide foam group for the safety population analyses. In Study 2, 1 patient was randomized to treatment with budesonide foam but received placebo during the study; this patient was included in the budesonide foam group for efficacy and safety analyses.
[b]Patients experiencing ≥1 AE were counted once and categorized by the most severe intensity AE.
[c]Percentage of patients in each analysis based on total population of the treatment group.
[d]AEs reported in ≥2% of patients in either treatment group.

with budesonide foam included decreased blood cortisol concentrations, adrenal insufficiency, headache, and nausea; UP was reported as an AE only in the placebo treatment arm (Table 2).

The incidence of serious AEs was similar between groups (budesonide foam, n = 5 [1.9%], vs placebo, n = 3 [1.1%]). Most serious AEs were not considered to be related to treatment with budesonide foam (eg, hypersensitivity [food allergy], arterial thrombosis limb, UC, abdominal pain) or placebo (eg, ectopic pregnancy, anemia, UC). However, 1 serious AE (acute generalized exanthematous pustulosis) was considered by the investigator to be related to treatment with budesonide foam and resolved without sequelae; the patient experiencing this event discontinued from the study.

Mean morning cortisol concentrations remained within normal levels after treatment with budesonide foam, although a transient decrease in mean cortisol concentrations was observed during twice-daily dosing, with a return to baseline concentrations observed by week 6 (Figure 3). Most of the patients treated with budesonide foam maintained normal total cortisol concentrations (>138 nmol/L) throughout the study and had normal responses to an ACTH challenge (Table 3). Normal total cortisol concentrations were apparent in >96% of patients in both treatment groups at baseline. During weeks 1 and 2 (twice-daily dosing), 85.2% and 84.0% of patients receiving budesonide foam maintained normal total cortisol concentrations. During weeks 4 and 6 (once-daily dosing), 92.8% and 94.2% of patients maintained normal total cortisol concentrations. The percentage of patients receiving placebo with normal total cortisol concentrations remained high (>97%) and virtually unchanged during the 6-week duration of the study. Normal responses to ACTH challenge at baseline (using the >18 μg/dL criterion) occurred in 98.1% and 98.9% of patients receiving budesonide foam and placebo, respectively. At week 6, the percentage of patients receiving budesonide foam or placebo with normal responses to ACTH challenge was 86.1% and 96.2%, respectively. No patients with abnormal ACTH challenge results

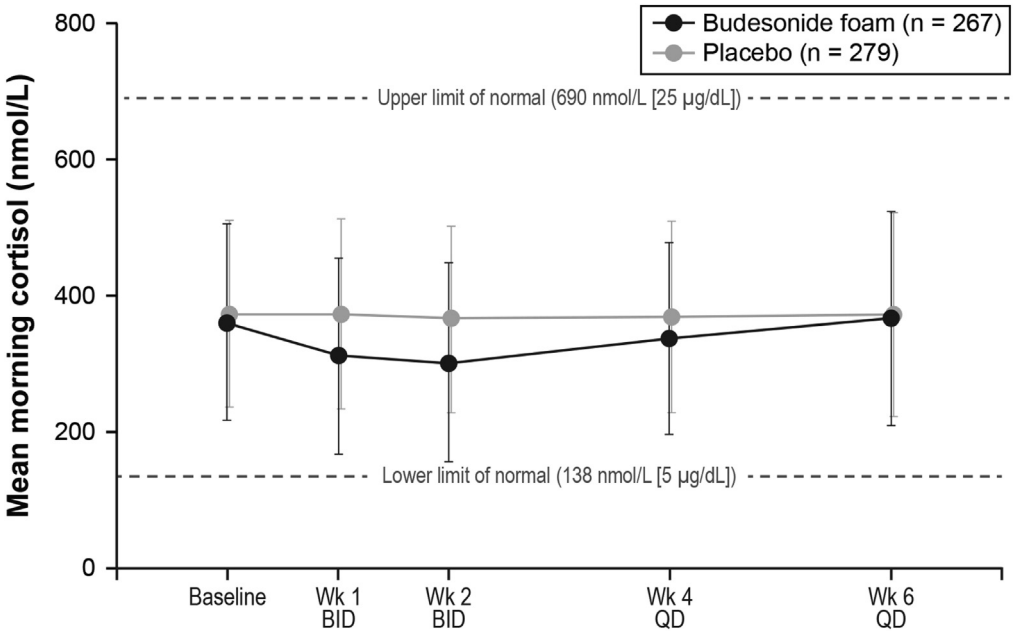

Figure 3. Mean morning serum cortisol concentrations. BID, twice daily; QD, once daily.

Table 3. Total Cortisol Concentrations and Normal Response to ACTH Challenge (Combined Analysis)

Parameter	Budesonide foam 2 mg/25 mL (n = 268)	Placebo (n = 278)
Total cortisol >5 μg/dL (138 nmol/L),[a] n/N[b] (%)		
Baseline	259/268 (96.6)	275/278 (98.9)
Week 1 (bid)	224/263 (85.2)	264/269 (98.1)
Week 2 (bid)	216/257 (84.0)	263/266 (98.9)
Week 4 (qd)	218/235 (92.8)	243/249 (97.6)
Week 6 (qd)	211/224 (94.2)	234/241 (97.1)
Normal response to ACTH challenge,[c] n/N[b] (%)		
Baseline	261/266 (98.1)	275/278 (98.9)
Week 6	186/216 (86.1)	226/235 (96.2)

bid, twice daily; qd, once daily.
[a]Lower limit of normal.
[b]Denominator N is the number of patients with a value at each given week during the study.
[c]Defined as a measurement of >18 μg/dL serum cortisol after ACTH challenge.

reported any other signs or symptoms potentially indicative of adrenal suppression. In addition, neither patients with AEs of decreased blood cortisol nor adrenal insufficiency reported any other AEs potentially indicative of adrenal suppression.

Glucocorticoid-related AEs—such as moon face, striae rubrae, flushing, fluid retention, mood changes, sleep changes, insomnia, acne, and hirsutism—were infrequently reported. Among budesonide foam–treated patients, 1 patient (0.4%) experienced insomnia, 1 patient experienced sleep disorder, and 1 patient experienced acne.

Pharmacokinetics

Low systemic exposure was observed in both studies, as shown by the substantial number of post-randomization plasma samples (39% in Study 1 and 27% in Study 2) from budesonide-treated patients that had budesonide concentrations below the limit of quantitation (0.03 ng/mL). Mean plasma budesonide concentrations, in samples above the limit of quantitation, were 0.37 ng/mL at week 1 (twice-daily treatment phase), and 0.18 ng/mL at week 6 (once-daily treatment phase) in Study 1; similar mean plasma budesonide concentrations were observed in Study 2. These plasma concentrations, along with the population-estimated mean maximum plasma concentration value across the 2 studies (0.57 ng/mL) and the highest budesonide plasma concentration observed in each of the studies (2.22 ng/mL in Study 1 and 1.96 ng/mL in Study 2), further demonstrate the low systemic exposure to budesonide. Budesonide systemic exposure (estimated area under the plasma concentration-time curve and maximum plasma concentration) did not correlate with decreased sensitivity to ACTH challenge at week 6, and systemic exposure was not statistically different between patients with normal vs abnormal ACTH challenge results (mean maximum plasma concentration, 0.53 ng/mL vs 0.79 ng/mL, respectively; $P = .27$). In total, these data suggest that budesonide foam did not have clinically relevant effects on the hypothalamic-pituitary-adrenal axis. In addition, systemic exposure was not affected by disease severity.

Discussion

In 2 identically designed, randomized, placebo-controlled studies, treatment with budesonide foam demonstrated significant benefit over placebo based on the rate of remission at week 6 among patients with active mild to moderate UP or UPS. Subgroup analyses of the combined data showed a consistent benefit for budesonide vs placebo across a variety of subgroups, defined by demographic and baseline disease characteristics. Notably, budesonide foam appeared to be efficacious in patients with diagnosed UP (disease extending approximately 15 cm from the anal verge) and UPS (disease extending up to 40 cm from the anal verge), and in patients with or without baseline mesalamine use. Significant treatment benefits were also observed in both studies for multiple prespecified secondary end points, including Mayo rectal bleeding subscore of 0 at week 6, rectal bleeding subscore of 0 at multiple scheduled assessments, and endoscopic improvement (Mayo endoscopy subscore of 0 or 1) at week 6. The stool frequency component of the primary end point of remission was defined as improvement or no change from baseline. Although there was no significant difference between groups in the Mayo stool frequency score, a budesonide treatment effect on the stool frequency score component would not necessarily be expected, given that between 34% and 43% of patients with UP or UPS have normal stools or constipation.[24,25] When specifically examined, the percentage of patients receiving budesonide foam who reported improvement in stool frequency score was numerically greater than the percentage of patients receiving placebo at all weeks across both studies. These findings are suggestive of stool frequency improvements at the population level. Although AEs related to changes in cortisol laboratory values were reported in a greater percentage of patients receiving budesonide foam compared with placebo, the incidence of other AEs was similar in the budesonide and placebo groups, and no clinically important safety signals were identified.

The current results confirm the findings of 2 other induction studies with budesonide foam in patients with active mild to moderate UP and UPS, which demonstrated that budesonide foam was similarly effective to hydrocortisone acetate enemas[20] and budesonide enemas.[21] When taken together, the results of the 2 current trials and earlier studies demonstrate that budesonide foam is an efficacious treatment for inducing remission in patients with mild to moderate UP and UPS.

The design of the trials incorporated dose reduction with a budesonide rectal foam (ie, twice-daily to once-daily dosing) that is consistent with the dosing of steroids in clinical practice. Clinical and endoscopic remission were

maintained through the switch from twice-daily to once-daily dosing. The initial twice-daily dosing regimen demonstrated rapid improvements in the rectal bleeding component of the Mayo score, as evidenced by significant differences vs placebo as early as the first week of treatment. Overall, the largest incremental improvement in rectal bleeding response to budesonide occurred within the first 2 weeks, during twice-daily dosing, and was further improved at week 4 and maintained at week 6, during once-daily dosing. It should be noted, however, that these analyses were not prespecified.

Although budesonide rectal foam exhibits high potency at the local application site, it has low systemic bioavailability due to rapid first-pass metabolism; this profile is predicted to decrease the incidence of steroid-related adverse effects as compared with rates for conventional corticosteroids. Low systemic bioavailability was also observed in the current study in patients with UP or UPS. Mean plasma budesonide concentrations, as well as the highest plasma concentrations observed in patients treated with budesonide, were similar to or lower than systemic exposures observed after administration of budesonide extended-release tablets (budesonide with multi-matrix system technology; Cosmo Pharmaceuticals SpA, Lainate, Italy) in healthy individuals.[26] The incidence of AEs and serious AEs was generally similar in the budesonide foam and placebo treatment groups. The overall safety profile of budesonide foam in the current study was consistent with results reported in trials of other budesonide formulations for patients with UC, including budesonide enemas and oral budesonide multi-matrix system technology.[27–29]

Reduction in plasma cortisol concentrations and abnormalities in adrenal responsiveness are known effects of systemic corticosteroids and are a potential concern during UC treatment.[30] As a second-generation corticosteroid, budesonide has been shown to cause less adrenal suppression compared with equivalent doses of conventional steroids, as measured by serum cortisol concentrations.[31] The effects of budesonide rectal foam on the hypothalamic-pituitary-adrenal axis in these studies were evaluated by review of laboratory assessments, including morning cortisol and ACTH challenge tests, and review of AEs and vital signs. It appears that budesonide rectal foam, at the dose and duration administered, had no clinical or biochemical consequences regarding adrenal gland suppression in most patients. Although morning cortisol values were decreased in a small percentage of patients, no AEs related to symptoms of adrenal insufficiency were reported in these patients. This finding could be due to the minimal reduction in serum cortisol values or to the direct pharmacologic effects of circulating budesonide. The results of ACTH stimulation testing further confirmed that biochemical adrenal suppression occurred in a small percentage of patients (eg, 14% for budesonide group compared with 4% in the placebo group at week 6). This suggests that plasma levels of budesonide were adequate to attenuate adrenal responsiveness to ACTH stimulation in only a small subset of patients and that, overall, the drug has a low probability of causing biochemical adrenal suppression. These minimal effects on the hypothalamic-pituitary-adrenal axis are in contrast with results from studies of other corticosteroid products for the treatment of UC.[6,32,33]

Compliance with the foam study medications was high for patients in each treatment group (budesonide 94%, placebo 97%). These levels of compliance are consistent with those reported in other studies that compared rectal foams containing budesonide or mesalamine with various liquid enema formulations and in which retention with rectal foams was better than retention with rectal liquid enemas.[21,34] Rectal foams were preferred to enemas by a large majority of patients, largely due to convenience and ease of use.[21] The high rates of compliance observed in our studies demonstrated that budesonide rectal foam can be used effectively by patients with distal forms of UC.

In conclusion, budesonide rectal foam 2 mg twice daily for 2 weeks and then once daily for 4 weeks was generally well tolerated and was superior to placebo in inducing remission in patients with active, mild to moderate UP and UPS. The dosage form allows for targeted delivery to the affected areas of the rectum/sigmoid colon in patients with distal forms of UC and allows for reduction from a 2-week phase of twice-daily dosing to a 4-week phase of once-daily dosing, reducing the potential for systemic steroid-related adverse effects. The safety profile of budesonide foam demonstrated in these studies is consistent with worldwide experience of budesonide products.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.01.037.

References

1. Ordás I, Eckmann L, Talamini M, et al. Ulcerative colitis. Lancet 2012;380:1606–1619.
2. Hanauer SB, Present DH, Rubin DT. Emerging issues in ulcerative colitis and ulcerative proctitis: individualizing treatment to maximize outcomes. Gastroenterol Hepatol (N Y) 2009;5:4–16.
3. Farmer RG, Easley KA, Rankin GB. Clinical patterns, natural history, and progression of ulcerative colitis. a long-term follow-up of 1116 patients. Dig Dis Sci 1993; 38:1137–1146.
4. Lichtenstein GR, Abreu MT, Cohen R; American Gastroenterological Association. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology 2006; 130:935–939.
5. Lewis JD, Gelfand JM, Troxel AB, et al. Immunosuppressant medications and mortality in inflammatory bowel disease. Am J Gastroenterol 2008;103: 1428–1435.

6. Kornbluth A, Sachar DB; The Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 2010;105:501–523.
7. Marshall JK, Thabane M, Steinhart AH, et al. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev 2010; 1:CD004115.
8. Loew BJ, Siegel CA. Foam preparations for the treatment of ulcerative colitis. Curr Drug Deliv 2012;9:338–344.
9. Brown J, Haines S, Wilding IR. Colonic spread of three rectally administered mesalazine (Pentasa) dosage forms in healthy volunteers as assessed by gamma scintigraphy. Aliment Pharmacol Ther 1997;11: 685–691.
10. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J 1955;2:1041–1048.
11. Truelove SC, Hambling MH. Treatment of ulcerative colitis with local hydrocortisone hemisuccinate sodium; a report on a controlled therapeutic trial. Br Med J 1958; 2:1072–1077.
12. Travis SP, Stange EF, Lémann M, et al. European evidence-based Consensus on the management of ulcerative colitis: current management. J Crohns Colitis 2008;2:24–62.
13. Brattsand R. Overview of newer glucocorticosteroid preparations for inflammatory bowel disease. Can J Gastroenterol 1990;4:407–414.
14. Edsbäcker S, Larsson P, Wollmer P. Gut delivery of budesonide, a locally active corticosteroid, from plain and controlled-release capsules. Eur J Gastroenterol Hepatol 2002;14:1357–1362.
15. Edsbäcker S, Bengtsson B, Larsson P, et al. A pharmacoscintigraphic evaluation of oral budesonide given as controlled-release (Entocort) capsules. Aliment Pharmacol Ther 2003;17:525–536.
16. Hanauer SB, Robinson M, Pruitt R, et al, U.S. Budesonide Enema Study Group. Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: a dose-ranging study. Gastroenterology 1998; 115:525–532.
17. Hartmann F, Stein J; The BudMesa-Study Group. Clinical trial: controlled, open, randomized multicentre study comparing the effects of treatment on quality of life, safety and efficacy of budesonide or mesalazine enemas in active left-sided ulcerative colitis. Aliment Pharmacol Ther 2010;32:368–376.
18. Biancone L, Gionchetti P, Del Vecchio Blanco G, et al. Beclomethasone dipropionate versus mesalazine in distal ulcerative colitis: a multicenter, randomized, double-blind study. Dig Liver Dis 2007;39:329–337.
19. Brunner M, Vogelsang H, Greinwald R, et al. Colonic spread and serum pharmacokinetics of budesonide foam in patients with mildly to moderately active ulcerative colitis. Aliment Pharmacol Ther 2005;22:463–470.
20. Bar-Meir S, Fidder HH, Faszczyk M, et al, The International Budesonide Study Group. Budesonide foam *vs.* hydrocortisone acetate foam in the treatment of active ulcerative proctosigmoiditis. Dis Colon Rectum 2003; 46:929–936.
21. Gross V, Bar-Meir S, Lavy A, et al, The International Budesonide Foam Study Group. Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis. Aliment Pharmacol Ther 2006; 23:303–312.
22. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317:1625–1629.
23. O'Brien PC, Shampo MA. Statistical considerations for performing multiple tests in a single experiment. 5. Comparing two therapies with respect to several endpoints. Mayo Clin Proc 1988;63:1140–1143.
24. Lennard-Jones JE, Cooper GW, Newell AC, et al. Observations on idiopathic proctitis. Gut 1962;3:201–206.
25. Rao SS, Read NW, Brown C, et al. Studies on the mechanism of bowel disturbance in ulcerative colitis. Gastroenterology 1987;93:934–940.
26. Brunner M, Ziegler S, Di Stefano AF, et al. Gastrointestinal transit, release and plasma pharmacokinetics of a new oral budesonide formulation. Br J Clin Pharmacol 2006;61:31–38.
27. Sandborn WJ, Travis S, Moro L, et al. Once-daily budesonide MMX® extended-release tablets induce remission in patients with mild to moderate ulcerative colitis: results from the CORE I study. Gastroenterology 2012; 143:1218–1226.
28. Travis SP, Danese S, Kupcinskas L, et al. Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomised CORE II study. Gut 2014;63:433–441.
29. Hanauer SB, Robinson M, Pruitt R, et al. Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: a dose-ranging study. U.S. Budesonide enema study group. Gastroenterology 1998; 115:525–532.
30. **Desramé J**, **Sabate JM**, Agher R, et al. Assessment of hypothalamic-pituitary-adrenal axis function after corticosteroid therapy in inflammatory bowel disease. Am J Gastroenterol 2002;97:1785–1791.
31. Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. Gut 1997;40:775–781.
32. Matts SG, Wharton BA, Kelleher J, Walters G. Adrenal cortical and pituitary function after intrarectal steroid therapy. Br Med J 1963;2:24–26.
33. Hammond A, Andus T, Gierend M, et al, German Budesonide Foam Study Group. Controlled, open, randomized multicenter trial comparing the effects of treatment on quality of life, safety and efficacy of budesonide foam and betamethasone enemas in patients with active distal ulcerative colitis. Hepatogastroenterology 2004;51: 1345–1349.
34. Cortot A, Maetz D, Degoutte E, et al. Mesalamine foam enema versus mesalamine liquid enema in active left-sided ulcerative colitis. Am J Gastroenterol 2008; 103:3106–3114.

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Conflicts of interest
These authors disclose the following: William Sandborn has received consulting fees from Salix Pharmaceuticals, Inc, and Santarus, Inc (a wholly owned subsidiary of Salix Pharmaceuticals, Inc). Brian Bosworth is a consultant, is on the speakers' bureau for, and has received research grants from Salix Pharmaceuticals, Inc. Salam Zakko serves as principal investigator on a variety of research protocols for, receives unrestricted grants from, serves on the speakers' bureau for, and holds stock in Salix Pharmaceuticals, Inc. Glenn Gordon serves as principal investigator on a variety of research protocols for, receives research grants from, and serves as a consultant to and on the speakers' bureau for Salix Pharmaceuticals, Inc. David Clemmons has consulted for Salix Pharmaceuticals, Inc. Pamela Golden, Robert Rolleri, Jing Yu, Andrew Barrett, Enoch Bortey, and Craig Paterson are full-time employees of and shareholders in Salix Pharmaceuticals, Inc. William Forbes is an officer, full-time employee of, and shareholder in Salix Pharmaceuticals, Inc.

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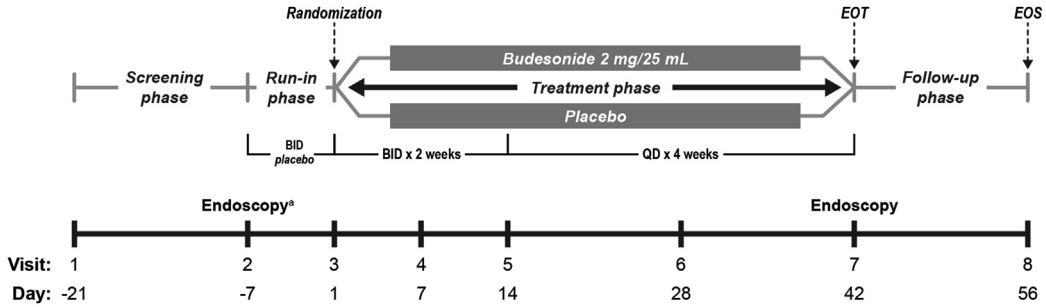
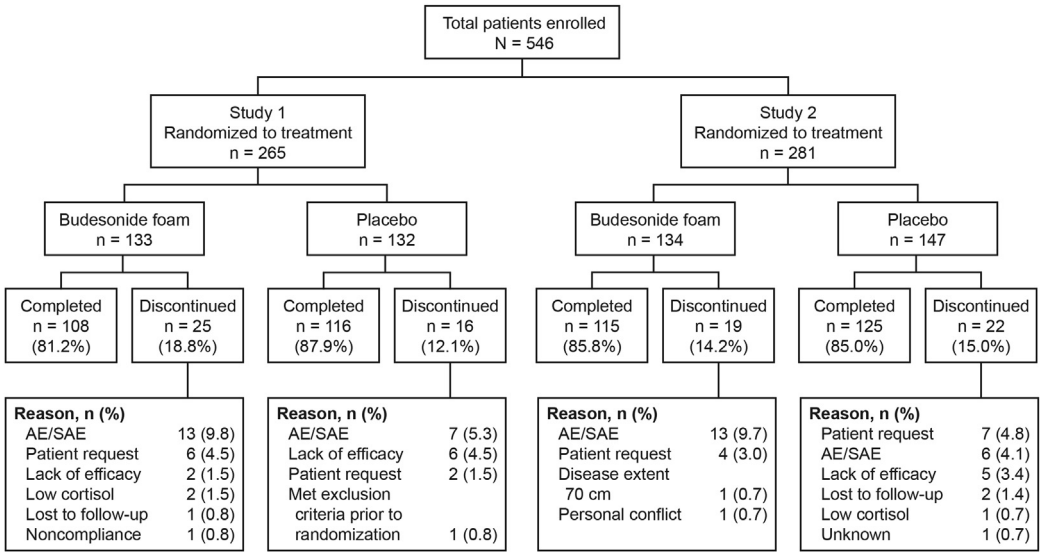
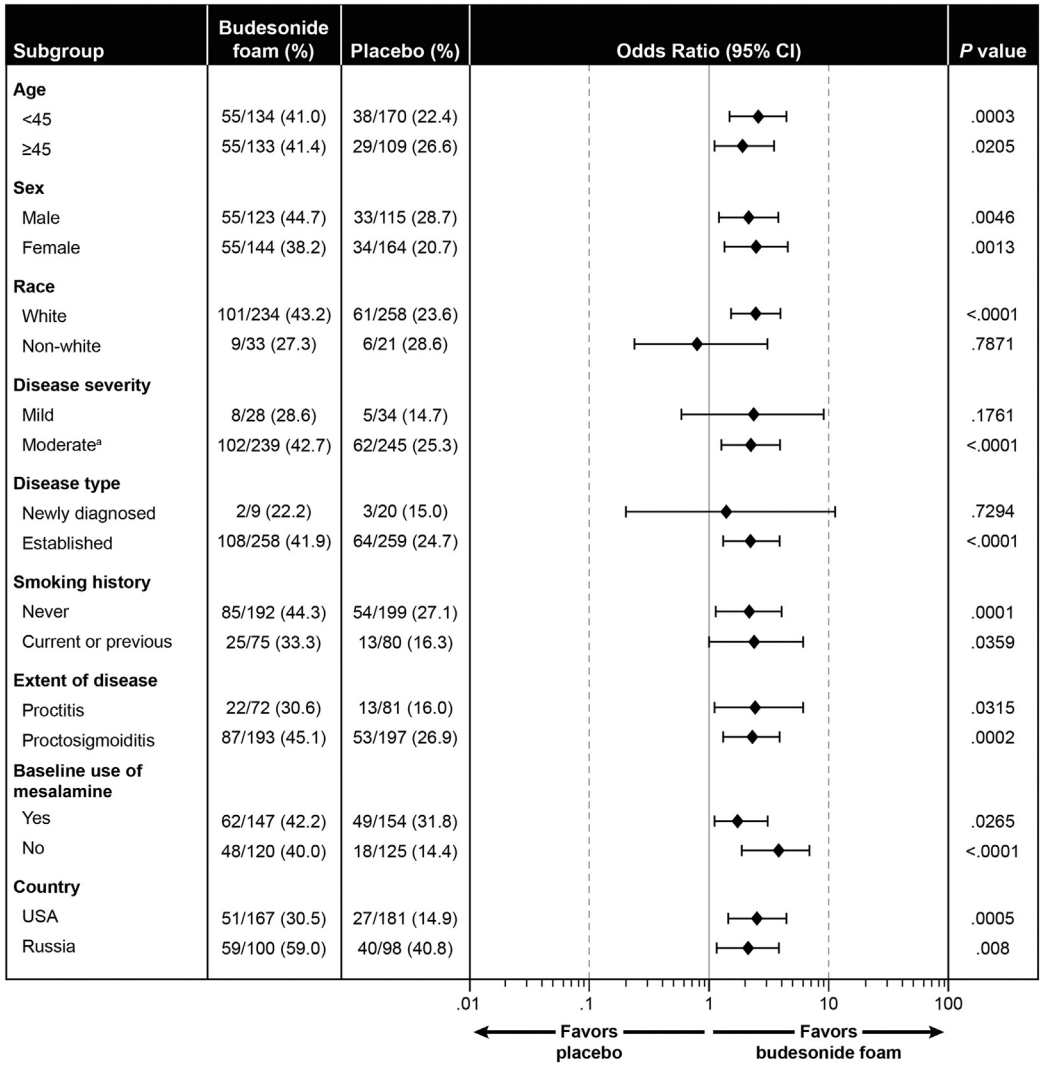


Supplementary Figure 1. Study design. [a]A colonoscopy was required for patients newly diagnosed or without a confirmed diagnosis of UC within 12 months of the screening visit. Colonoscopy, if needed, was performed no more than 10 days, and no less than 4 days, before randomization. If a colonoscopy was not required, patients were scheduled for sigmoidoscopy 4 to 7 days before randomization. BID, twice daily; EOS, end of study; EOT, end of treatment; QD, once daily.



Supplementary Figure 2. Study disposition. SAE, serious adverse event.



Supplementary Figure 3. Patients achieving remission at week 6 (primary efficacy measure) by subgroup in the combined study population. Remission defined as endoscopy score ≤ 1, rectal bleeding score $= 0$, and improvement or no change from baseline in stool frequency subscales of the Mayo score. [a]In Study 2, moderate severity of disease included 2 patients treated with budesonide foam who had severe disease at baseline.