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Effects of Apremilast, an Oral Inhibitor of Phosphodiesterase 4, in a Randomized Trial of Patients With Active Ulcerative Colitis

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BACKGROUND & AIMS: New oral therapeutic agents are needed for patients with ulcerative colitis (UC) who are unresponsive or intolerant to conventional therapy.

METHODS: We performed a double-blind, phase 2 trial of adults with active UC for 3 months or more who were naïve to biologic therapy or had been failed by, could not tolerate, or had contraindications to conventional therapies. The study was performed at 61 sites in 14 countries (screening from January 2015 through May 2017). Patients were randomly assigned to groups given apremilast 30 mg (n = 57), apremilast 40 mg (n = 55), or placebo (n = 58) twice daily for 12 weeks; patients were then randomly assigned to groups that received apremilast, 30 or 40 mg twice daily, for an additional 40 weeks. Endoscopies were performed and biopsies were collected during the screening phase, at week 12, and at week 52. Blood and fecal samples were also collected and analyzed throughout the study. The primary endpoint was clinical remission at week 12, defined as a total Mayo score of 2 or less, with no individual subscore above 1.

RESULTS: Clinical remission was achieved at week 12 by 31.6% of patients in the 30 mg apremilast group and 12.1% of patients in the placebo group ($P = .01$). However, only 21.8% of patients in the 40 mg apremilast group achieved clinical remission at week 12 ($P = .27$ compared with placebo). Differences in clinical remission between the 30 mg and 40 mg apremilast groups were associated with differences in endoscopic improvement. Both apremilast groups had similar improvements from baseline in Mayo score components (stool frequency score, rectal bleeding score, physician's global assessment). The 30 mg and 40 mg apremilast groups had greater median percent reductions in C-reactive protein (measured by a high-sensitivity blood test) and fecal calprotectin through week 12 than the placebo group. At week 52, clinical remission was achieved by 40.4% of patients initially assigned to the apremilast 30 mg group and 32.7% of patients initially assigned to the apremilast 40 mg group. The most frequent apremilast-associated adverse events were headache and nausea.

CONCLUSIONS: Although the primary endpoint of clinical remission was not met in this phase 2 trial, a greater proportion of patients with active UC who received apremilast (30 mg or 40 mg) had improvements in clinical and endoscopic features, and markers of inflammation, at 12 weeks. Clinical remission was maintained to week 52 in up to 40% of patients who continued apremilast until that time point. ClinicalTrials.gov no: NCT02289417

Key words: Biologic-Naïve; TMS; IBD; CRP.

Abbreviations used in this paper: AE, adverse event; CI, confidence interval; CRP, C-reactive protein; FCP, fecal calprotectin; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; MES, Mayo endoscopic score; MMS, modified Mayo score; PDE4, phosphodiesterase 4; PMS, partial Mayo score; RBS, rectal bleeding subscore; TMS, total Mayo score; TNF-α, tumor necrosis factor α; UC, ulcerative colitis.

Most current article

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Ulcerative colitis (UC), a chronic relapsing inflammatory condition of the large intestine, has no known cure. Current therapies include nonbiologics (mesalamine, corticosteroids, immunosuppressants), biologics (infliximab, adalimumab, golimumab, vedolizumab), and an oral immunomodulatory agent (tofacitinib). Many patients do not respond to or are intolerant of available therapy. Biologic and oral immunomodulatory treatments are associated with adverse events (AEs) such as serious infections and malignancies. More specific, better-tolerated agents are needed for patients with UC.

Apremilast, an oral small-molecule phosphodiesterase 4 (PDE4) inhibitor, acts intracellularly to modulate inflammatory mediators.[1] The important enzyme PDE4 regulates inflammatory response by increasing production of proinflammatory mediators (ie, tumor necrosis factor α [TNF-α], interleukin [IL]-23) and decreasing production of anti-inflammatory mediators (ie, IL-10).[1,2] Apremilast inhibits TNF-α and matrix metalloproteinase 3 production in lamina propria mononuclear cells of patients with inflammatory bowel disease.[3] Apremilast 30 mg twice daily is approved for treatment of patients with active psoriatic arthritis, moderate to severe plaque psoriasis, or oral ulcers associated with Behçet's disease.

This phase 2 study evaluated the efficacy and safety of apremilast treatment in patients with active UC.

What You Need to Know

Background

Targeted and better-tolerated oral treatments are needed for ulcerative colitis (UC). Apremilast inhibits production of tumor necrosis factor and matrix metalloproteinase 3 in lamina propria mononuclear cells from patients with inflammatory bowel diseases.

Findings

Patients with UC given apremilast had greater improvements, from baseline, in total Mayo score, clinical remission, biomarkers, and histological and endoscopic responses than did patients given placebo at week 12. Remission was maintained for 52 weeks.

Implications for patient care

Many patients with UC do not respond to conventional therapies. Apremilast improved outcomes of biologic-naïve patients who had been failed by, were intolerant to, or had a contraindication to conventional therapies.

Materials and Methods

Study Design

This multicenter study consisted of a 12-week double-blind, randomized, placebo-controlled period followed by a 40-week double-blind active-treatment extension (Figure 1). The study was conducted at 61 investigational sites in 14 countries. Patients were randomly assigned at baseline (1:1:1) to receive oral apremilast (Celgene Corporation, Summit, NJ) 30 mg or 40 mg twice daily or placebo for 12 weeks. Randomization was stratified by concomitant oral corticosteroid use and prior immunosuppressant exposure. At week 12, patients receiving placebo were randomized to apremilast 30 mg or 40 mg for an additional 40 weeks (until week 52). Patients receiving apremilast 30 mg continued the same dose until week 52 if they had a $\geq$20% decrease in total Mayo score (TMS) at week 12. Patients receiving apremilast 30 mg without a $\geq$20% decrease in TMS at week 12 or who were initially randomized to 40 mg received 40 mg until week 52 (Figure 1).

The 30-mg dose was evaluated due to its demonstrated efficacy and safety profiles in psoriatic diseases. The 40-mg dose was used to explore potential additive therapeutic and dose-related effects. As apremilast was not previously evaluated in UC, patients were dose titrated in 10-mg increments daily over the first 8 days of treatment to mitigate known side effects (ie, gastrointestinal disturbances, headache) seen in previous studies.[4–6]

The trial was sponsored and conducted by Celgene Corporation. An external data monitoring committee was in place to evaluate any safety signal. Members of an external committee of consultants and trial investigators were involved in the protocol development and data analysis and interpretation. The trial protocol was approved by the institutional review board/ethics committee for each participating institution (protocol number: CC-10004-UC-001), and the study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines. All authors had access to the study data and reviewed and approved the final report.

Participants

Adults ($\geq$18 years of age) with a UC diagnosis for $\geq$3 months were eligible if they provided written informed consent and met criteria for documented moderate to severe active UC (ie, TMS $\geq$6 to $\leq$11 and Mayo endoscopic score [MES] $\geq$2). All patients were biologic-naïve and failed, were intolerant of, or had contraindications to 1 or more conventional UC therapies: oral aminosalicylates (ie, mesalamine compounds, sulfasalazine), budesonide, systemic corticosteroids, or immunosuppressants (ie, 6-mercaptopurine, azathioprine, methotrexate). Patients diagnosed with Crohn's disease or other colitis subtypes (ie, ischemic, microscopic, radiation, or diverticular disease-associated colitis) were

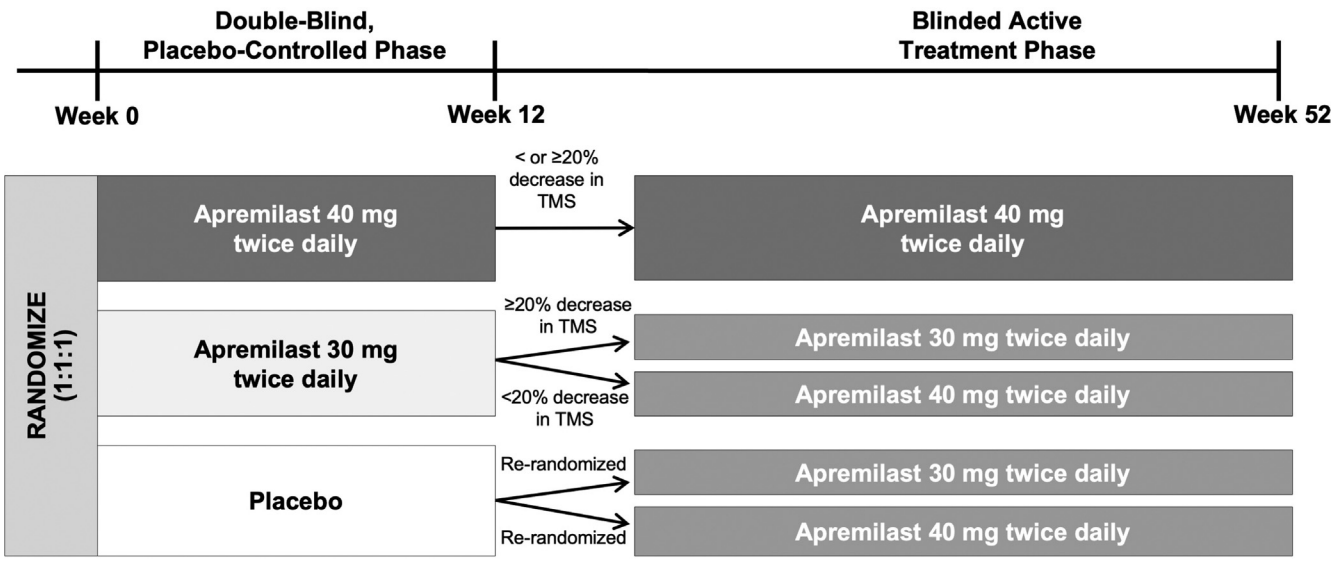

Figure 1. Study design. For the active treatment phase, patients assigned to receive placebo at baseline were rerandomized at week 12 to receive twice-daily apremilast 30 mg or apremilast 40 mg. Patients assigned to receive the 30-mg dose at baseline who failed to achieve ≥20% decrease from baseline TMS at week 12 received the 40-mg dose; all others (who achieved ≥20% decrease from baseline TMS at week 12) continued the 30-mg dose. All patients assigned to apremilast 40 mg at baseline continued to receive this treatment.

excluded. Additional exclusion criteria are described in Supplementary Table 1.

Concomitant and Prohibited Medications

Patients could receive concurrent treatment with stable doses (≥14 days) of oral sulfasalazine or mesalamine and stable doses (≥3 weeks) of oral corticosteroids (≤20 mg/d of prednisone or equivalent). Patients could not use immunosuppressants (ie, 6-mercaptopurine, azathioprine, methotrexate, mycophenolic acid, tacrolimus, cyclosporine) or any biologic agent (ie, TNF inhibitors).

Endoscopy Assessments

Endoscopy was performed during the screening phase, at week 12, and at week 52, or at the early termination visit if it occurred before week 52. Endoscopies were read by a central reader blinded to treatment allocation and sequence.

Intestinal Mucosal Biopsies

Mucosal biopsies were performed during the screening phase, at week 12, and at week 52, or at the early termination visit if it occurred before week 52 once the endoscopies were complete. Biopsies were taken from the most inflamed area of the rectum or rectosigmoid junction, while avoiding ulcerated mucosa. Biopsies taken postbaseline were from the same location as the baseline biopsy.

Blood and Tissue Sampling

To measure C-reactive protein (CRP) and fecal calprotectin (FCP) concentrations, blood and fecal samples were obtained at baseline and weeks 2 (fecal sample only), 4, 8, and 12 during the placebo-controlled phase and at weeks 36 and 52 during the active treatment phase. CRP was detected using a high-sensitivity technique (high-sensitivity CRP [hsCRP]); FCP was measured using validated assays.

Primary and Secondary Outcomes

The primary efficacy endpoint was the proportion of patients achieving clinical remission at week 12, defined as a TMS ≤2 with no individual subscore >1. Clinical remission was also assessed at week 52. Secondary efficacy and endoscopic endpoints at week 12 included the proportions of patients achieving the following: clinical remission in modified Mayo score (MMS) ≤2 (range: 0–9, based on stool frequency, rectal bleeding subscore [RBS], and endoscopic assessment), with no individual subscore >1; endoscopic response (a decrease from baseline MES ≥1); endoscopic remission (MES of 0); TMS clinical response (decrease from baseline in TMS ≥3 and ≥30%; decrease in RBS ≥1 or absolute RBS ≤1); and MMS clinical response (decrease from baseline in MMS ≥3 and ≥25%; reduction in RBS ≥1 or absolute RBS ≤1). The proportion of patients achieving clinical remission by partial Mayo score (PMS), defined as a PMS ≤2 with no individual subscore >1, was evaluated at week 8. Exploratory endpoints for the proportion of patients achieving histological remission (Geboes score <2) and mucosal healing (MES ≤1 and Geboes score <2) were

assessed at week 12. Exploratory biomarkers included hsCRP and FCP at each assessment point through weeks 12 and 52, and the proportions of patients achieving hsCRP <3.0 mg/L (in patients with baseline hsCRP >3.0 mg/L)[7] and FCP ≤250 μg/g (in patients with baseline FCP >500 μg/g).[8] Safety outcomes included the nature, frequency, and severity of AEs and their relationship to treatment. The number of patients who discontinued treatment due to AEs and frequency of clinically significant changes in physical examination findings, vital signs, and laboratory parameters were determined.

Statistical Analysis

Descriptive statistics were used to summarize baseline demographic and clinical characteristics and safety outcomes. Efficacy analyses were conducted using the intention-to-treat population, which comprised all patients randomized according to the protocol who received ≥1 dose of study treatment. For binary endpoints, patients with missing data or treatment failures (ie, protocol-prohibited initiation or dose increase of concomitant UC medications, colectomy or ostomy) were considered nonresponders. For continuous endpoints, missing data were imputed by the last-observation-carried-forward approach; data after treatment failures were considered missing. The proportion of patients achieving clinical remission at week 12 (primary endpoint) was compared by 2-sided Cochran-Mantel-Haenszel test (0.1 significance level) and stratified by the randomization stratification factors. Results are presented as differences from placebo with 95% confidence intervals (CIs). Tests for the primary endpoint were performed hierarchically to adjust for multiplicity, with apremilast 40 mg vs placebo compared first, followed by apremilast 30 mg vs placebo.

To evaluate changes in exploratory biomarkers, percent change from baseline in hsCRP and FCP was compared using analysis of covariance based on rank-transformed data, with treatment group and randomization stratification as factors and baseline value as a covariate. Missing data were imputed using the last-observation-carried-forward approach.

A sample size of 147 patients (49 per group) would yield 80% power to detect an estimated 20% difference (30% vs 10%) between apremilast and placebo in the proportion of patients achieving clinical remission at week 12, based on a 2-group chi-square test with a 2-sided significance level of 0.1. Assuming a 10% dropout rate before week 12, ∼165 patients (55 per group) were planned to be randomized.

Results

From January 2015 to May 2017, 307 patients were screened. Reasons for screen failure are outlined in Supplementary Table 2. In total, 170 patients underwent randomization and were included in the intention-to-treat population; 57 patients received apremilast 30 mg, 55 received apremilast 40 mg, and 58 received placebo. Completing the 12-week placebo-controlled phase were 53 (93%) patients receiving apremilast 30 mg, 52 (95%) receiving apremilast 40 mg, and 51 (88%) receiving placebo. The 52-week treatment phase was completed by 64% of patients initially randomized to placebo, 81% initially randomized to apremilast 30 mg, and 71% initially randomized to apremilast 40 mg (Supplementary Figure 1). Baseline demographic and clinical characteristics were balanced across patient groups (Table 1); baseline mean TMS and MES indicated patients had active disease.

Efficacy Outcomes

The primary endpoint (clinical remission at week 12) was achieved by 21.8% (n = 12 of 55) of patients

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Placebo (n = 58)	Apremilast	
		30 mg Twice daily (n = 57)	40 mg Twice daily (n = 55)
Age, *y*	42.9 ± 14.0	40.1 ± 13.5	43.4 ± 14.9
Male	33 (57)	39 (68)	34 (62)
Duration of ulcerative colitis, *y*	6.9 ± 7.0	6.2 ± 5.4	8.6 ± 10.3
Disease in rectum and sigmoid only	14 (24)	14 (25)	15 (27)
Use of corticosteroids	17 (29)	14 (25)	12 (22)
Previous exposure to immunosuppressant therapy[a]	17 (29)	18 (32)	16 (29)
Total Mayo score	8.2 ± 1.7	8.5 ± 1.6	8.1 ± 1.7
Endoscopy subscore	2.6 ± 0.5	2.7 ± 0.5	2.6 ± 0.5
hsCRP, *mg/L*	11.29 ± 19.20	7.33 ± 10.07	8.53 ± 12.15
hsCRP ≥3 *mg/L*	34/58 (58.6)	30/55 (54.5)	34/55 (61.8)
Fecal calprotectin, μg/g	3,261.6 ± 5,103.8	3,215.1 ± 4,538.5	3,143.8 ± 3,694.2

Values are mean ± SD, n (%), or n/n (%).
hsCRP, high-sensitivity C-reactive protein.
[a]Includes methotrexate, azathioprine, and 6-mercaptopurine.

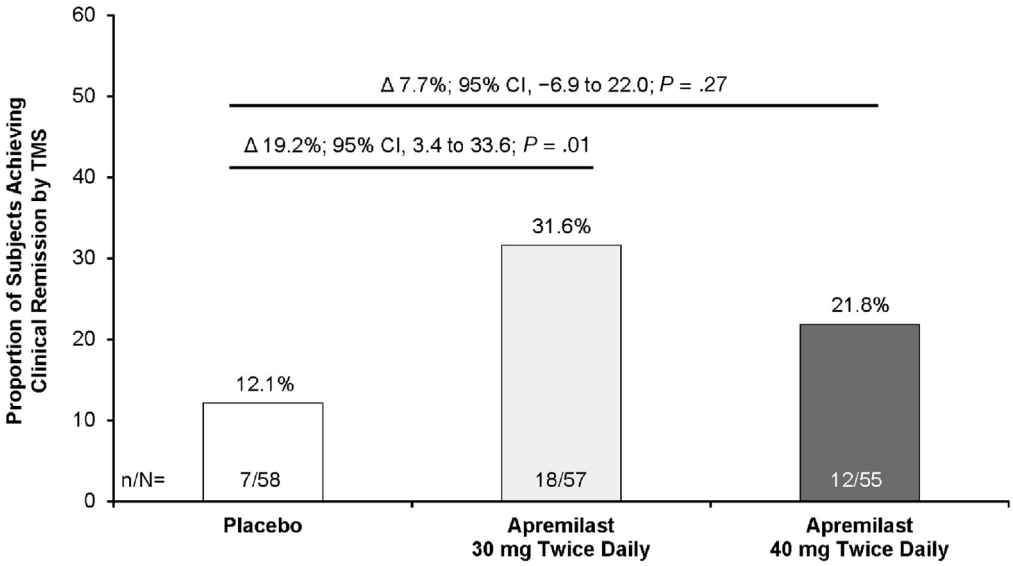

Figure 2. Proportion of patients achieving clinical remission by TMS (defined as a TMS ≤2 with no individual subscore >1) at week 12 (primary outcome). Includes patients in the intention-to-treat population; missing values imputed as nonresponse.

receiving apremilast 40 mg vs 12.1% (n = 7 of 58) receiving placebo (difference, 7.7%; 95% CI, −6.9% to 22.0%; $P = .269$). Because of the hierarchical, stepdown testing procedure to control the type I error rate at the 0.1 level for the primary endpoint, the formal apremilast 30 mg vs placebo comparison could not be performed. However, a nominally higher proportion of patients receiving apremilast 30 mg achieved TMS clinical remission (31.6% [n = 18 of 57]) vs placebo ($P = .014$) (Figure 2). Results were consistent for MMS remission at week 12 (difference, 24.8%; 95% CI, 7.5%–40.1%; $P = .005$) for apremilast 30 mg (Table 2).

A greater proportion of patients receiving apremilast 30 mg, but not 40 mg, achieved MES endoscopic response vs placebo (difference, 32.0%; 95% CI, 13.8%–47.4%; $P < .001$) (Table 2). At week 12, MES endoscopic remission rates with either dose were not different from placebo. TMS clinical response at week 12 was achieved by a greater proportion of patients receiving apremilast 40 mg, but not 30 mg, vs placebo (difference, 19.4%; 95% CI, 1.1%–36.0%; $P = .040$). MMS-based clinical response rates at week 12 were generally similar to TMS. PMS clinical remission was achieved as early as week 4 (Supplementary Figure 2); at week 8, PMS clinical

Table 2. Efficacy Outcomes at Week 12 and Week 8

Assessment	Placebo (n = 58)	Apremilast 30 mg Twice daily (n = 57)	Apremilast 40 mg Twice daily (n = 55)
Week 12			
Total Mayo score clinical remission[a]	7 (12.1)	18 (31.6)	12 (21.8)
Difference from placebo; 95% CI		19.2; 3.4 to 33.6; $P = .01$	7.7; −6.9 to 22.0; $P = .27$
Modified Mayo score clinical remission[b]	11 (19.0)	25 (43.9)	15 (27.3)
Difference from placebo; 95% CI		24.8; 7.5 to 40.1; $P = .005$	6.0; −9.8 to 21.6; $P = .45$
Mayo endoscopic subscore response[c]	24 (41.4)	42 (73.7)	26 (47.3)
Difference from placebo; 95% CI		32.0; 13.8 to 47.4; $P < .001$	3.7; −14.4 to 21.5; $P = .69$
Total Mayo score clinical response[d]	27 (46.6)	35 (61.4)	37 (67.3)
Difference from placebo; 95% CI		14.6; −3.6 to 31.5; $P = .12$	19.4; 1.1 to 36.0; $P = .04$
Modified Mayo score clinical response[e]	27 (46.6)	36 (63.2)	37 (67.3)
Difference from placebo; 95% CI		16.7; −1.4 to 33.5; $P = .08$	19.8; 1.5 to 36.4; $P = .04$
Week 8			
Partial Mayo score clinical remission[f]	19 (32.8)	27 (47.4)	29 (52.7)
Difference from placebo; 95% CI		14.6; −3.3 to 31.4; $P = .12$	18.1; −0.3 to 34.9; $P = .05$

Values are n (%), unless otherwise indicated.
CI, confidence interval.
[a]A total Mayo score ≤2 with no individual subscore >1.
[b]A modified Mayo score ≤2 with no individual subscore >1.
[c]A decrease from baseline of ≥1 point in the Mayo endoscopic subscore.
[d]A decrease from baseline of ≥3 points and ≥30% in the total Mayo score, along with a reduction in the rectal bleeding subscore ≥1point or an absolute rectal bleeding score ≤1.
[e]A decrease from baseline of ≥2 points and ≥25% in the modified Mayo score, along with a reduction in the rectal bleeding subscore ≥1 point or an absolute rectal bleeding subscore ≤1.
[f]A partial Mayo score ≤2, with no individual subscore >1.

remission was achieved by numerically more patients receiving apremilast 30 mg (difference, 14.6%; 95% CI, −3.3% to 31.4%; $P = .117$) or 40 mg (difference, 18.1%; 95% CI, −0.3% to 34.9%; $P = .053$) than placebo. Histological remission was achieved by a greater proportion of apremilast 30 mg (difference, 14.6%; 95% CI, −3.0% to 31.0%; $P = .10$) and 40 mg (difference 12.5%; 95% CI, −5.2% to 29.2%; $P = .17$) patients vs placebo (Supplementary Figure 3). Mucosal healing was achieved by more patients receiving apremilast 30 mg vs placebo (difference, 17.1%; 95% CI, 1.1%–32.0%; $P = .033$) (Supplementary Figure 4).

At week 12, only 12 of 53 patients initially randomized to apremilast 30 mg and continuing the study beyond week 12 had doses uptitrated to 40 mg through week 52 (having experienced <20% decrease in TMS at week 12, per study protocol); minimal benefit was observed with dose escalation. Therefore, the apremilast 30 mg/40 mg and apremilast 30 mg/30 mg groups were combined for the week 52 analyses. At week 52, TMS clinical remission was achieved by 40.3% of patients initially randomized to apremilast 30 mg, 32.7% initially randomized to apremilast 40 mg, 23.1% initially randomized to placebo and switched to apremilast 30 mg at week 12, and 40.0% initially randomized to placebo and switched to apremilast 40 mg at week 12 (Supplementary Table 3).

hsCRP and FCP Biomarkers

In patients receiving apremilast 30 mg or 40 mg, greater median percent decreases from baseline in serum hsCRP vs placebo were detected at week 4 and sustained to week 12 (Supplementary Figure 5). At week 12, median percent decrease in hsCRP for apremilast 30 mg was greater than placebo (difference, −30.7%; 95% CI, −57.3% to −2.3%; $P = .034$) but not 40 mg (difference, −19.5%; 95% CI, −51.8% to 8.9%; $P = .166$). In patients who had hsCRP >3 at baseline, an hsCRP <3.0 mg/L was achieved by a greater proportion of patients receiving apremilast 30 mg at week 4 ($P = .018$), week 8 ($P = .027$), and week 12 ($P = .032$) and with 40 mg at week 12 ($P = .035$) (Supplementary Figure 6) vs placebo. Median percent decreases from baseline in serum hsCRP were generally maintained through week 52 across treatment groups (Supplementary Figure 7).

Likewise, greater median percent decreases from baseline in FCP were detected at week 2 for apremilast 30 mg (difference, −42.3%; 95% CI, −73.5% to −8.8%; $P = .007$) and 40 mg (difference, −38.3%; 95% CI, −71.7% to −6.3%; $P = .015$) vs placebo and were sustained at weeks 4 and 8 (Supplementary Figure 8). At week 12, median percent decrease in FCP for apremilast 30 mg (difference, −7.9%; 95% CI, −34.0% to 0.8%; $P = .118$) or 40 mg (difference, −7.1%; 95% CI; −32.1% to 0.9%; $P = .138$) was not different from placebo (Supplementary Figure 8). In patients with FCP >500 μg/g, FCP ≤250 μg/g was achieved by more patients receiving apremilast 30 mg at week 4 ($P = .011$), week 8 ($P = .005$), and week 12 ($P = .014$) and 40 mg at week 8 ($P = .044$), but not at week 12, vs placebo (Supplementary Figure 9). Median percent decreases from baseline in FCP were maintained through week 52 in patients initially randomized to apremilast 30 mg and 40 mg (Supplementary Figure 10).

Safety

Over 12 weeks, 31 of 58 patients receiving placebo (53.4%), 28 of 57 receiving apremilast 30 mg (49.1%), and 35 of 55 receiving apremilast 40 mg (63.6%) experienced ≥1 AE (Table 3). The most frequently reported AEs (≥5% in either apremilast group) were headache, nausea, pharyngitis, back pain, abdominal pain, and asthenia. Headache, a common AE reported with apremilast, was reported more frequently in patients receiving apremilast vs placebo. One patient receiving apremilast 40 mg experienced headache (severe) leading to withdrawal. Nausea was the most frequently reported gastrointestinal AE. Diarrhea was reported by more placebo than apremilast 30 mg and 40 mg patients (3.4% vs 1.8% and 0.0%). Mild depression was reported in 1 placebo patient and moderate depression in 1 apremilast 40 mg patient; no apremilast 30 mg patients reported depression.

Serious AEs occurred in 2 (3.4%) placebo patients and 1 (1.8%) apremilast 40 mg patient. Two patients receiving placebo experienced UC worsening, which resolved in both patients; and 1 patient discontinued treatment. One patient receiving apremilast 40 mg who had a history of hepatobiliary disease experienced pancreatitis deemed by investigators to be unrelated to study treatment; pancreatitis resolved with treatment and without sequelae but the patient discontinued treatment. In the placebo group, 3 additional patients discontinued treatment, including 1 with heart failure and atrial fibrillation; 1 with abdominal cramps, vomiting, and diarrhea; and 1 with iron-deficiency anemia, worsening UC, and gastroesophageal reflux. No deaths occurred during the study.

Weight loss was reported as an AE in 1 placebo patient and 2 apremilast 40 mg patients but no apremilast 30 mg patients. No substantial decreases in weight were observed after 12 weeks of treatment; median percent changes in body weight from baseline were 0.6% with placebo, −1.2% with apremilast 30 mg, and −0.9% with apremilast 40 mg. One placebo patient had an observed weight loss ≥10%. Laboratory abnormalities were infrequent and occurred with similar frequency in the placebo and apremilast groups (Table 3).

In all, 72.3% of patients receiving apremilast 30 mg and 83.8% receiving apremilast 40 mg reported an AE, and serious AEs were reported by 6 (7.2%) and 8

Table 3. Treatment-Emergent Adverse Events and Select Laboratory Assessments Through Week 12

		Apremilast	
	Placebo (n = 58)	30 mg Twice daily (n = 57)	40 mg Twice daily (n = 55)
Patients			
Any adverse event	31 (53.4)	28 (49.1)	35 (63.6)
Any serious adverse event	2 (3.4)	0 (0.0)	1 (1.8)[a]
Any adverse event leading to drug withdrawal	5 (8.6)	0 (0.0)	1 (1.8)
Any adverse event leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Adverse event in ≥5% of patients			
Headache	4 (6.9)	12 (21.1)	14 (25.5)
Nausea	5 (8.6)	3 (5.3)	6 (10.9)
Nasopharyngitis	1 (1.7)	4 (7.0)	2 (3.6)
Abdominal pain	1 (1.7)	3 (5.3)	0 (0.0)
Asthenia	2 (3.4)	3 (5.3)	1 (1.8)
Ulcerative colitis	3 (5.2)	0 (0.0)	0 (0.0)
Back pain	1 (1.7)	0 (0.0)	3 (5.5)
Selected laboratory assessments			
Alanine aminotransferase, >3× *ULN*	0/55 (0.0)	0/56 (0.0)	0/52 (0.0)
Creatinine, >1.7× *ULN*	0/56 (0.0)	0/56 (0.0)	0/52 (0.0)
Hemoglobin			
Male: <105 *g/L*, female: <85 *g/L*	1/55 (1.8)	1/55 (1.8)	1/53 (1.9)
Male: >185 *g/L*, female: >170 *g/L*	0/55 (0.0)	0/55 (0.0)	0/53 (0.0)
Leukocytes $<1.5 \times 10^9$/L	0/55 (0.0)	0/55 (0.0)	0/53 (0.0)
Neutrophils $<1.0 \times 10^9$/L	0/55 (0.0)	1/55 (1.8)	0/53 (0.0)
Platelets $<75 \times 10^9$/L	0/55 (0.0)	0/54 (0.0)	0/53 (0.0)

Values are n (%) or n/N (%).
ULN, upper limit of normal.
[a]Pancreatitis.

(10.0%) patients receiving apremilast 30 mg and 40 mg, respectively. Supplementary Table 4 lists the most common AEs and serious AEs through week 52.

Discussion

The efficacy and safety of apremilast 30 mg and 40 mg twice daily were assessed in patients with UC. A numerically greater proportion of patients receiving apremilast 40 mg achieved the primary endpoint of TMS remission at week 12; however, this did not reach statistical significance. With the prespecified hierarchical, stepdown testing procedure, formal apremilast 30 mg vs placebo comparison was not performed, although a nominal difference was seen between patients receiving apremilast 30 mg and placebo.

Although a higher proportion of patients receiving apremilast 30 mg vs 40 mg achieved TMS remission (31.6% vs 21.8%), the overall data do not indicate a meaningful difference in treatment responses between the apremilast dose groups. The difference between dose groups in TMS remission rates was due to differences in week 12 endoscopy improvements. A post hoc analysis indicated that a higher proportion of patients in both treatment groups achieved MES ≤1 vs placebo, and the highest responses were observed with 30 mg (30 mg: 56.1%; 40 mg: 34.5%; placebo: 24.1%). A higher proportion of patients receiving apremilast 30 mg and 40 mg achieved an improvement in nonendoscopic components of the TMS vs placebo patients (as indicated by RBS ≤1, stool frequency score ≤1, and Physician's Global Assessment score ≤1) (Supplementary Table 3). Histological remission (Geboes score <2) was achieved by a higher proportion of patients in both dose groups vs placebo. PMS clinical remission was evident as early as week 4 for both dose groups. Changes from baseline were observed as early as 2 weeks for FCP and 4 weeks for hsCRP for both dose groups, and decreases were maintained through week 52. In addition, both dose groups maintained TMS remission through week 52.

In psoriatic arthritis[4–6] and psoriasis[9,10] studies of apremilast, the most common AEs were diarrhea, nausea, headache, upper respiratory tract infection, and nasopharyngitis. Rates of overall AEs and the most common AEs decreased with long-term exposure. Rates of serious AEs, including major cardiac events, malignant neoplasm, and serious opportunistic infections, were low and did not increase over time.[11] In the current study, the observed AEs were consistent with the known safety profile of apremilast. Headache was the most frequent AE and was reported by more patients receiving apremilast than placebo. Although diarrhea is commonly associated with UC,[12–14] the incidence of nausea and diarrhea was less frequent over 52 weeks in the present study (6%–11% [both doses]) than in studies conducted in patients with psoriatic arthritis (14%–16% over 24 weeks [30-mg dose])[4–6] or psoriasis (16%–19% over 16 weeks [30-mg

dose]).[9,10] Among patients with psoriatic disease, apremilast has been associated with weight loss and an increased, but rare, risk of depression.[15] In this study, 2 patients receiving apremilast 40 mg experienced weight loss, but no apremilast patients experienced weight loss ≥10%. One patient receiving apremilast 40 mg reported depression.

Enrolled patients were biologic-naïve and had failed, were intolerant to, or had a contraindication to conventional UC therapies, including oral mesalamine, budesonide, systemic corticosteroids, or immunosuppressants (ie, methotrexate). Treatment options for managing such patients are limited.[16] A substantial proportion of patients who fail treatment with mesalamine initiate corticosteroids, as per current treatment guidelines.[16] In 1 study, 45% of patients were receiving corticosteroids following initial UC diagnosis and 38% of corticosteroid users became steroid dependent.[17] UC treatment guidelines suggest thiopurine for maintaining corticosteroid-free remission; patients not adequately responding to this regimen should then be considered candidates for biologic therapy.[16] However, lack of clear evidence supporting the efficacy of these treatments and potential safety issues pose challenges for long-term use,[16,18–20] highlighting the need for additional treatment options before biologic therapy that address patient needs and balance safety with efficacy.

Conclusions

In this phase 2 study, the primary endpoint was not met; however, apremilast led to numerically greater outcomes in TMS clinical remission, biomarkers, and histological and endoscopic response vs placebo over 12 weeks. These improvements were maintained through week 52 at both doses. Safety and tolerability were consistent with previous studies in other indications.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.12.032.

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Conflicts of interest
These authors disclose the following: Silvio Danese reports receiving honoraria as a speaker, consultant, and/or advisory board member from AbbVie, Allergan, Biogen Idec, Boehringer Ingelheim, Celgene Corporation, Celltrion, Ferring, Hospira, Janssen, Johnson & Johnson, Merck, Merck Sharp & Dohme, Mundipharma, Pfizer, Sandoz, Takeda, Tigenix, UCB Pharma, and Vifor. Markus F. Neurath has received honoraria as a consultant from Bionorica, Celgene Corporation, e.Bavarian Health, Boehringer Ingelheim, Hexal, Hoffmann-La Roche, Index Pharmaceuticals, Janssen-Cilag, Merck Sharp & Dohme, Pentax Europe, PPM, Takeda, and Tillots; and received honoraria as a speaker from AbbVie, Falk Foundation, Janssen-Cilag, and Pentax Europe. Salam F. Zakko has received grant/research support from Celgene Corporation. Corey A. Siegel has served as a consultant and advisory board member for AbbVie, Amgen, Celgene Corporation, Eli Lilly, Janssen, Pfizer, Prometheus Sandoz, Sebela, and Takeda; as a speaker for CME activities for AbbVie, Janssen, Pfizer, and Takeda; and has received grant support from AbbVie, AHRQ (1R01HS021747-01), Crohn's & Colitis Foundation, Janssen, Pfizer, and Takeda. Remo Panaccione has received honoraria as a scientific advisory board member from Abbott/AbbVie, Amgen, Janssen, Merck, Pfizer, Prometheus, Salix, Shire, Takeda, and Warner Chilcott; and received honoraria as a consultant and speaker from Abbott/AbbVie, Amgen, Aptalis, AstraZeneca, Baxter, Bristol-Myers Squibb, Centocor, Elan/Biogen Idec, Eisai, Ferring, GlaxoSmithKline, Janssen, Merck, Millennium, Pfizer, Proctor & Gamble, Prometheus, Schering-Plough, Shire, Takeda, UCB Pharma, and Warner Chilcott. Xiaojiang Zhan, Keith Usiskin, and Denesh Chitkara were employees of Celgene Corporation at the time of study conduct. The remaining authors disclose no conflicts.

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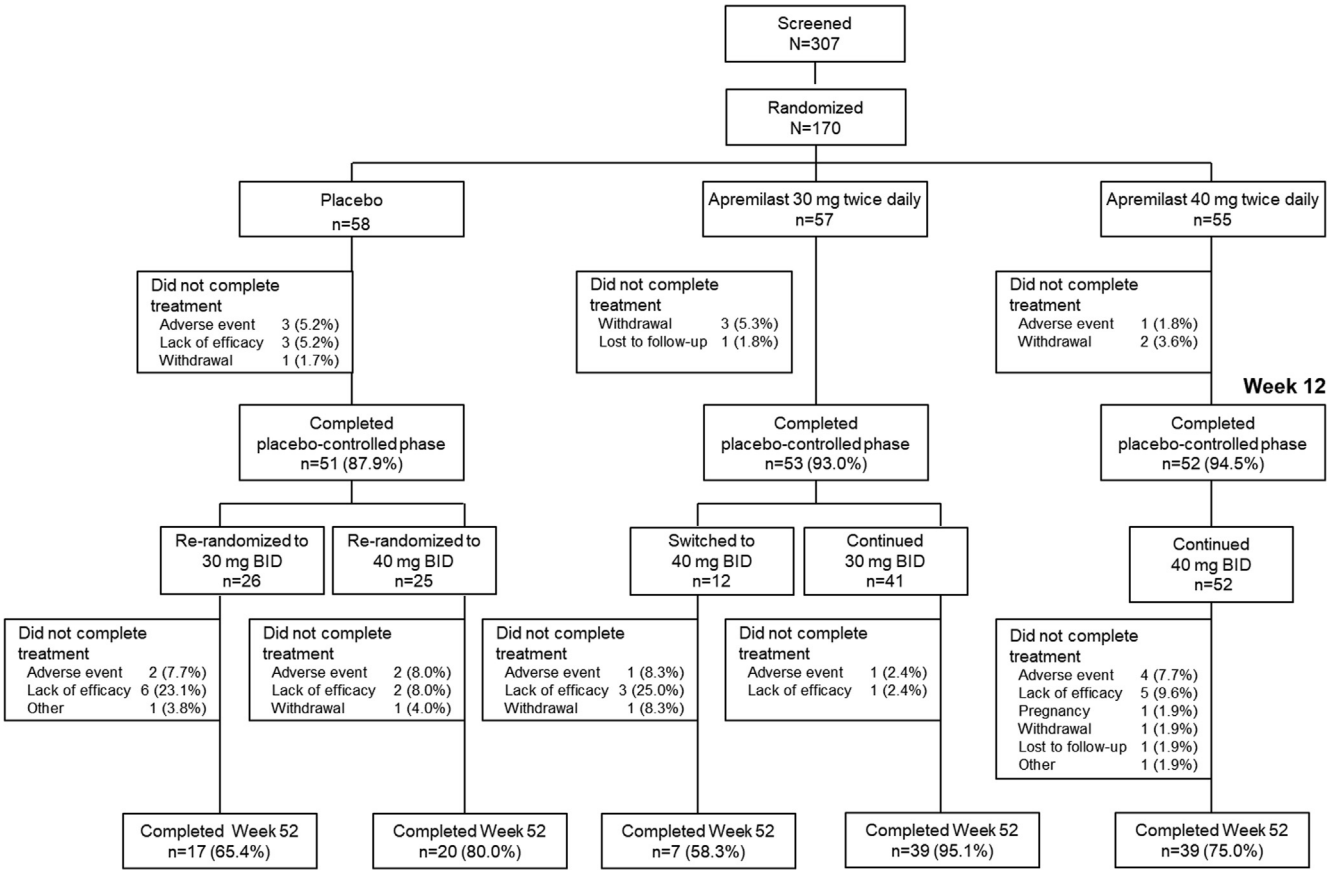
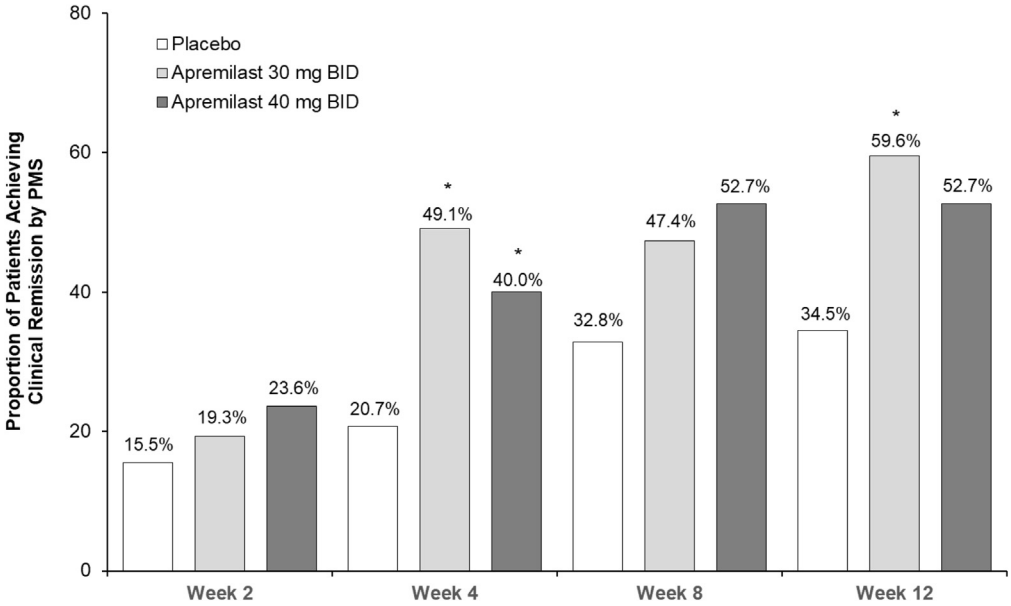
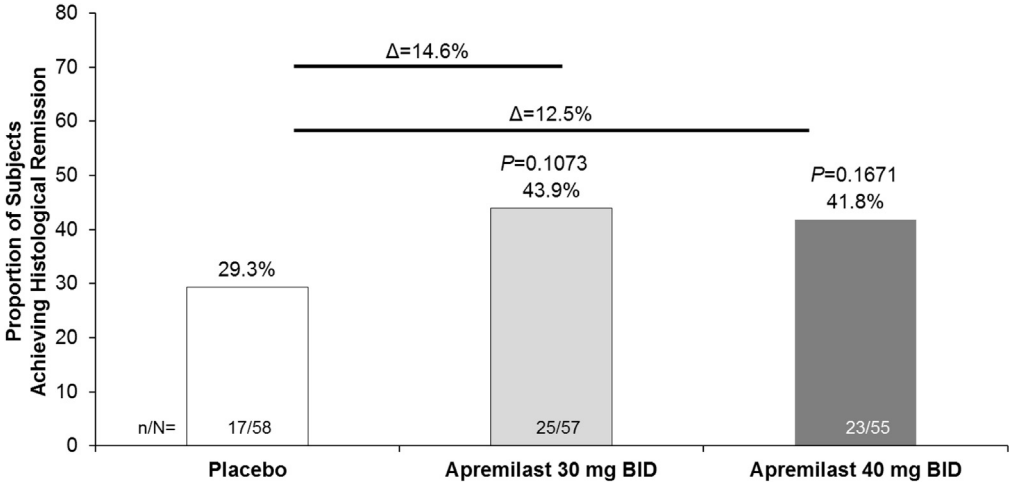


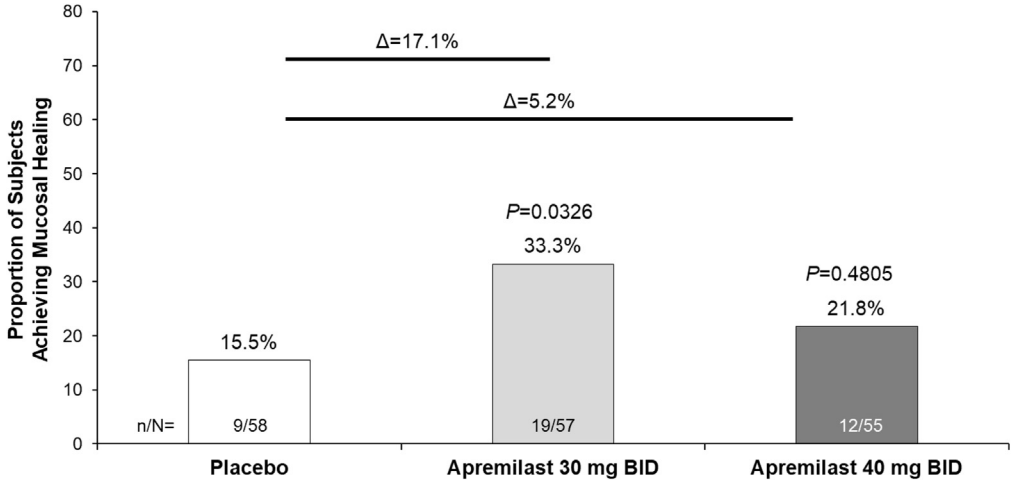
Supplementary Figure 1. Patient disposition through week 52.



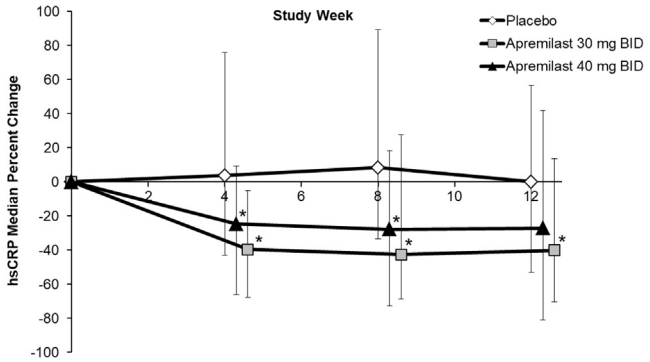
Supplementary Figure 2. Proportion of patients achieving clinical remission by partial Mayo score (PMS) through week 12. PMS ≤ 2 with no individual subscore >1. *$P < .05$ vs placebo. Difference from placebo at week 12 for apremilast 30 mg: 25.7%; 95% confidence interval, 7.4% to 41.9%; $P = .01$. Difference from placebo at week 12 for apremilast 40 mg: 16.7%; 95% confidence interval, -1.6% to 33.6%; $P = .08$. BID, twice daily.



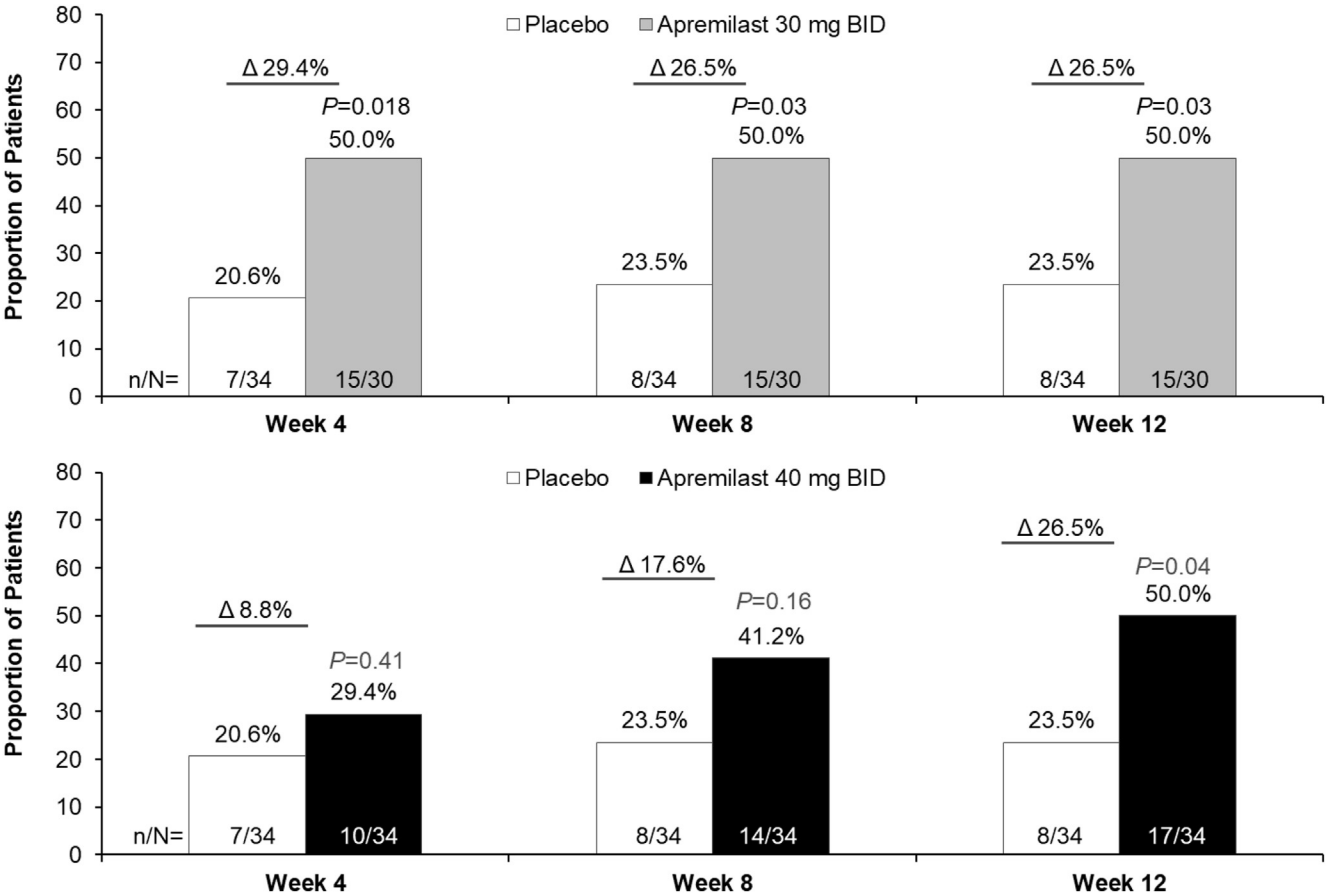
Supplementary Figure 3. Proportion of patients achieving histological remission (Geboes score <2) at week 12. Remission is defined as Geboes score <2. Includes patients in the intention-to-treat population; missing values imputed using nonresponder imputation. BID, twice daily.



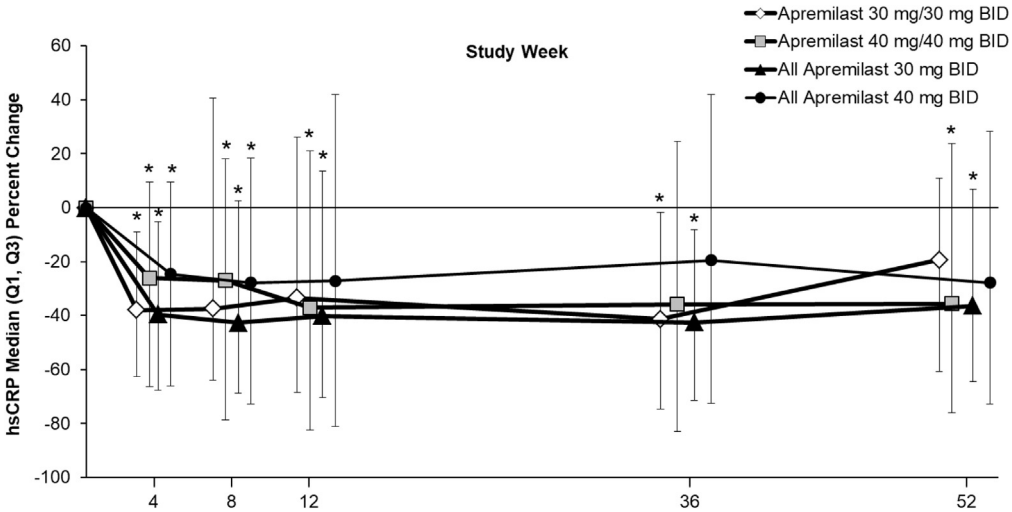
Supplementary Figure 4. Proportion of patients achieving mucosal healing at week 12. Mucosal healing is defined as Mayo endoscopic score (MES) ≤1 AND Geboes score <2. Includes patients in the intention-to-treat population; missing values imputed using nonresponder imputation. BID, twice daily.



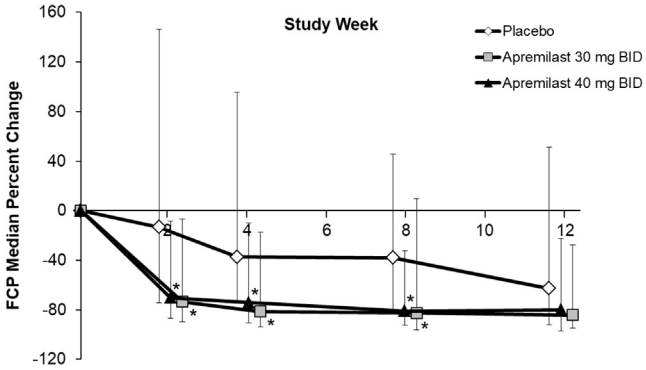
Supplementary Figure 5. Median percent change from baseline in high-sensitivity C-reactive protein (hsCRP) through week 12. Includes patients in the intention-to-treat population; missing values imputed as last observation carried forward. *$P \leq .05$ vs placebo. Week 12 difference from placebo in median percent change from baseline for apremilast 30 mg: −30.7%; 95% confidence interval, −57.3% to −2.3%; $P = .03$. Week 12 difference from placebo in median percent change from baseline for apremilast 40 mg: −19.5%; 95% confidence interval, −51.8% to 8.9%; $P = .17$. BID, twice daily.



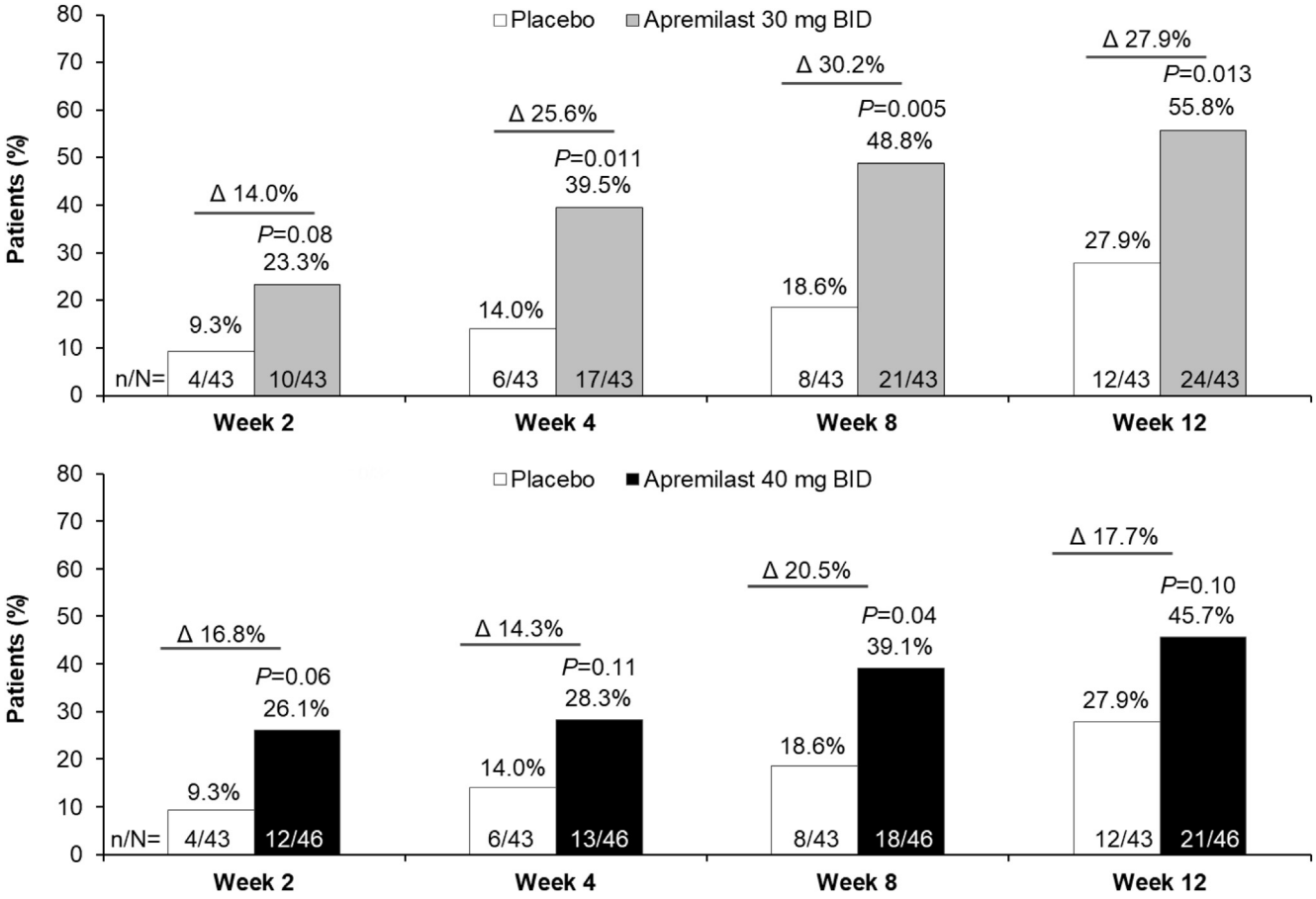
Supplementary Figure 6. Proportions of patients with high-sensitivity C-reactive protein (hsCRP) <3.0 mg/L through week 12. Includes patients in the intention-to-treat population with baseline hsCRP >3.0 mg/L; missing values imputed using nonresponder imputation. BID, twice daily.



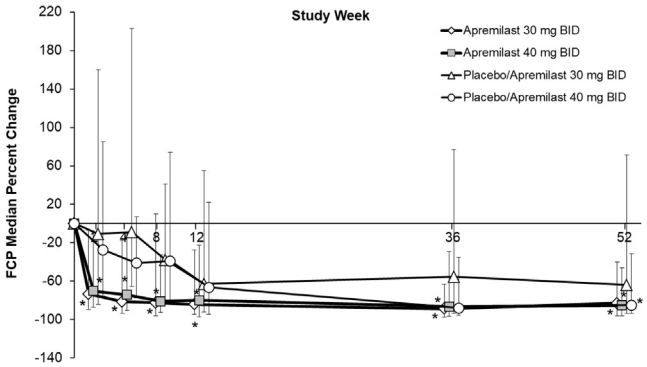
Supplementary Figure 7. Median percent change from baseline in high-sensitivity C-reactive protein (hsCRP) through week 52. Includes patients in the intention-to-treat population; missing values imputed as last observation carried forward. *$P < .05$ vs baseline. Apremilast 30 mg/30 mg twice daily (BID) (n = 41) and apremilast 40 mg/40 mg BID (n = 42) groups include patients who were responders at week 12 (≥20% decrease in total Mayo score) and continued on initially randomized treatment with apremilast 30 mg or 40 mg, respectively. All apremilast 30 mg (n = 57) and all apremilast 40 mg (n = 55) groups include all patients as initially randomized, regardless of responder status at week 12. Patients randomized to apremilast 30 mg BID who were nonresponders at week 12 had doses uptitrated to 40 mg BID through week 52. Q, quarter.



Supplementary Figure 8. Median percent change from baseline in fecal calprotectin (FCP) through week 12. Includes patients in the intention-to-treat population; missing values imputed as last observation carried forward. *$P < .05$ vs placebo. Week 12 difference from placebo in median percent change from baseline for apremilast 30 mg: −7.9%; 95% confidence interval, −34.0% to 0.8%; $P = .12$. Week 12 difference from placebo in median percent change from baseline for apremilast 40 mg: −7.1%; 95% confidence interval, −32.1% to 0.9%; $P = .14$. BID, twice daily.



Supplementary Figure 9. Proportions of patients with fecal calprotectin (FCP) $\leq$250 μg/g through week 12. Includes patients in the intention-to-treat population with baseline FCP $>$500 μg/g; missing values imputed using nonresponder imputation. BID, twice daily.



Supplementary Figure 10. Median percent change from baseline in fecal calprotectin (FCP) through week 52. Includes patients in the intention-to-treat population; missing values imputed as last observation carried forward. *$P < .05$ vs baseline. Apremilast 30 mg (n = 57) and apremilast 40 mg (n = 55) groups include all patients as initially randomized, regardless of responder status at week 12. Patients randomized to apremilast 30 mg twice daily (BID) who were nonresponders at week 12 (n = 12) had doses uptitrated to 40 mg BID through week 52.

Supplementary Table 1. Additional Exclusion Criteria

Exclusionary treatments
Any prior treatment with mycophenolic acid, tacrolimus, sirolimus, cyclosporine, or thalidomide
Used intravenous corticosteroids or corticosteroid enemas or suppositories within 2 wk of screening, immunosuppressants (azathioprine, 6-mercaptopurine, or methotrexate) within 8 wk, or topical mesalamine within 2 wk
Comorbidities/medical history
Ulcerative colitis restricted to the distal ≤15 cm (eg, ulcerative proctitis)
Clinical signs suggestive of fulminant colitis or toxic megacolon
Evidence of pathogenic enteric infection
History of suicide attempt at any time or hospitalization for a major psychiatric illness within 3 mo of randomization
History of any major cardiac condition, event, or surgery within 6 mo of screening
Active current or history of recurrent infection or a major infection requiring hospitalization or treatment with an antibiotic (intravenous or oral) within 4 wk of screening
Women who were pregnant or breastfeeding
Any condition that could affect oral drug absorption including gastric resection, gastroparesis, or bariatric surgery

Supplementary Table 2. Eligibility Criteria Failure

Reason for eligibility criteria failure	Patients not randomized (n = 137 of 307)
TMS ≥6 to ≤11 (range: 0–12) at baseline, before randomization	25 (8.1)
Endoscopic subscore ≥2 (range: 0–3) on Mayo score determined within 10 d of randomization	17 (5.5)
Endoscopic subscore ≥2 (range: 0–3) on Mayo score determined within 10 d of randomization	14 (4.6)
TMS ≥6 to ≤11 (range: 0–12) at baseline, before randomization	9 (2.9)
FCBP must have negative pregnancy test at screening and baseline visit; while on IP and for ≥28 d after last dose, FCBP must use an approved contraceptive option: • Option 1: Hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring), intrauterine device, tubal ligation, or partner's vasectomy OR • Option 2: Male or female condom (latex condom or nonlatex condom NOT made out of natural [animal] membrane [eg, polyurethane]), PLUS 1 additional barrier method: (1) diaphragm with spermicide, (2) cervical cap with spermicide, or (3) contraceptive sponge with spermicide	7 (2.3)
TMS ≥6 to ≤11 (range: 0–12) at baseline, before randomization	6 (2.0)
Must be able to adhere to study visit schedule and other protocol requirements	6 (2.0)
FCBP must have negative pregnancy test at screening and the baseline visit; while on IP and for ≥28 d after last dose, FCBP must use an approved contraceptive options: • Option 1: Hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring), intrauterine device, tubal ligation, or partner's vasectomy OR • Option 2: Male or female condom (latex condom or nonlatex condom NOT made out of natural [animal] membrane [eg, polyurethane]), PLUS 1 additional barrier method: (1) diaphragm with spermicide, (2) cervical cap with spermicide, or (3) contraceptive sponge with spermicide	5 (1.6)
UC restricted to the distal ≤15 cm (eg, ulcerative proctitis)	4 (1.3)
Clinical signs suggestive of fulminant colitis or toxic megacolon	4 (1.3)
Must be able to adhere to study visit schedule and other protocol requirements	4 (1.3)
Endoscopic subscore ≥2 (range: 0–3) on Mayo score determined within 10 d of randomization	3 (1.0)
Clinical signs suggestive of fulminant colitis or toxic megacolon	3 (1.0)
History of any clinically significant neurologic, renal, hepatic, gastrointestinal, pulmonary, metabolic, cardiovascular, psychiatric, endocrine, hematologic disorder, or any other medical condition that, in investigator's opinion, precludes study participation	3 (1.0)
Known active current or history of recurrent bacterial, viral, fungal, mycobacterial, or other infections (including but not limited to tuberculosis and atypical mycobacterial disease and herpes zoster), HIV, or any major episode of infection requiring hospitalization or treatment with IV or oral antibiotics within 4 wk of screening	3 (1.0)
Must be able to adhere to study visit schedule and other protocol requirements	2 (0.7)
Diagnosis of Crohn's disease, indeterminate colitis, ischemic colitis, microscopic colitis, radiation colitis, or diverticular disease-associated colitis	2 (0.7)
UC restricted to the distal ≤15 cm (eg, ulcerative proctitis)	2 (0.7)
Must understand and voluntarily sign informed consent document before any study-related assessments/procedures conducted	2 (0.7)
Evidence of pathogenic enteric infection	2 (0.7)
Clinical signs suggestive of fulminant colitis or toxic megacolon	1 (0.3)
Positive for hepatitis C antibody (therefore, not eligible for study participation)	1 (0.3)
Must have had therapeutic failure, been intolerant to, or have contraindication to ≥1 of following: oral aminosalicylates (ie, mesalamine compounds or sulfasalazine), budesonide, systemic corticosteroids, or immunosuppressants (ie, MTX, azathioprine, or 6-MP)	1 (0.3)
Clinically significant abnormality, based on chest radiograph, with at least postanterior view (must be taken within 12 wk of screening [visit 1] or during screening visit); additional lateral view strongly recommended but not required	1 (0.3)
Evidence of pathogenic enteric infection	1 (0.3)
Use of oral corticosteroids within 6 wk of randomization	1 (0.3)
Known active current or history of recurrent bacterial, viral, fungal, mycobacterial, or other infections (including but not limited to tuberculosis and atypical mycobacterial disease and herpes zoster), HIV, or any major episode of infection requiring hospitalization or treatment with IV or oral antibiotics within 4 wk of screening	1 (0.3)
History of congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease)	1 (0.3)
History of malignancy, except for treated (ie, cured): a. Basal cell or squamous cell in situ skin carcinomas b. Cervical intraepithelial neoplasia or carcinoma in situ of cervix with no evidence of recurrence within previous 5 years	1 (0.3)

Supplementary Table 2. Continued

Reason for eligibility criteria failure	Patients not randomized (n = 137 of 307)
Diagnosis of UC with duration of ≥3 months before screening	1 (0.3)
Oral aminosalicylates permitted during the study, provided that treatment duration is ≥6 wk before randomization with stable dose of ≥14 d before randomization; oral aminosalicylate dose must remain stable through week 20 or early termination	1 (0.3)
Diagnosis of Crohn's disease, indeterminate colitis, ischemic colitis, microscopic colitis, radiation colitis, or diverticular disease–associated colitis	1 (0.3)
History of colorectal cancer or colorectal dysplasia	1 (0.3)
Use of immunosuppressants (azathioprine, 6-MP, or MTX) within 8 wk of randomization	1 (0.3)
History of any clinically significant neurologic, renal, hepatic, gastrointestinal, pulmonary, metabolic, cardiovascular, psychiatric, endocrine, hematologic disorder or disease, or any other medical condition that, in investigator's opinion, precludes study participation	1 (0.3)
Must understand and voluntarily sign informed consent document before any study-related assessments/procedures conducted	1 (0.3)
Required to have colonoscopy if not performed within 12 mo of randomization	1 (0.3)
Oral aminosalicylates permitted during study, provided that treatment duration is ≥6 wk before randomization with stable dose of ≥14 d before randomization; oral aminosalicylate dose must remain stable through week 20 or early termination	1 (0.3)

NOTE. Values are n (%). Percentages are based on all screened patients. A patient may fail >1 eligibility criterion. For rescreened patients who were not randomized, only the eligibility criteria failed at the last screening are summarized. Eligibility criteria failed are sorted in descending order of frequency.
6-MP, 6-mercaptopurine; FCBP, women of childbearing potential; HIV, human immunodeficiency virus; IP, investigational product; IV, intravenous; MTX, methotrexate; TMS, total Mayo score; UC, ulcerative colitis.

Supplementary Table 3. Proportion of Patients Achieving Clinical Remission by TMS at Week 52 (Nonresponder Imputation)

	Placebo/APR 30 mg twice daily (n = 26)	Placebo/APR 40 mg twice daily (n = 25)	APR 30 mg twice daily (n = 57)	APR 40 mg twice daily (n = 55)
TMS clinical remission	6 (23.1)	10 (40.0)	23 (40.4)	18 (32.7)

NOTE. Values are n (%). Clinical remission denotes a TMS ≤2 with no individual subscore >1. The APR 30 mg twice daily group included 12 patients who were switched to APR 40 mg twice daily at week 12 and 41 patients who continued on APR 30 mg twice daily through week 52.
APR, apremilast; TMS, total Mayo score.

Supplementary Table 4. Treatment-Emergent Adverse Events Through Week 52

	Apremilast	
	30 mg twice daily (n = 83)	40 mg twice daily (n = 80)
Overview of adverse events		
Any adverse event	60 (72.3)	67 (83.8)
Any serious adverse event	6 (7.2)	8 (10.0)
Any adverse event leading to drug withdrawal	3 (3.6)	9 (11.3)
Any adverse event leading to death	0 (0.0)	0 (0.0)
Adverse event in ≥5% of patients		
Headache	17 (20.5)	23 (28.8)
Nausea	8 (9.6)	9 (11.3)
Nasopharyngitis	6 (7.2)	5 (6.3)
Diarrhea	5 (6.0)	6 (7.5)
Arthralgia	4 (4.8)	5 (6.3)
Upper respiratory infection	4 (4.8)	4 (5.0)
Cough	0 (0.0)	5 (6.3)
Serious adverse events		
Rectal abscess	0 (0.0)	1 (1.3)
Urinary tract infection	1 (1.2)	0 (0.0)
Acute myocardial infarction	1 (1.2)	0 (0.0)
Congestive cardiomyopathy	1 (1.2)	0 (0.0)
Ulcerative colitis	1 (1.2)	3 (3.8)
Crohn's disease	0 (0.0)	1 (1.3)
Diarrhea	0 (0.0)	1 (1.3)
Pancreatitis	0 (0.0)	1 (1.3)
Cholecystitis	1 (1.2)	0 (0.0)
Renal colic	1 (1.2)	2 (2.5)

NOTE. Values are n (%). Includes all apremilast-exposure data, regardless of when the apremilast exposure started (at week 0 or week 12). The 30-mg group includes data during the period of 30 mg treatment for patients who received apremilast 30 mg only, patients who initially received apremilast 30 mg and then switched to apremilast 40 mg at week 12, and patients who initially received placebo and then switched to apremilast 30 mg at week 12. The 40-mg group includes data during the period of 40 mg treatment for patients who received apremilast 40 mg only and patients who initially received placebo and then switched to apremilast 40 mg at week 12.