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Abatacept for Crohn's Disease and Ulcerative Colitis

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BACKGROUND & AIMS: The efficacy of abatacept, a selective costimulation modulator, in Crohn's disease (CD) and ulcerative colitis (UC) is unknown. **METHODS:** Four placebo-controlled trials evaluated the efficacy and safety of abatacept as induction (IP) and maintenance (MP) therapy in adults with active, moderate-to-severe CD (CD-IP; CD-MP) and UC (UC-IP1; UC-MP). In CD-IP and UC-IP1, 451 patients with CD and 490 patients with UC were randomized to abatacept 30, 10, or 3 mg/kg (according to body weight) or placebo, and dosed at weeks 0, 2, 4, and 8. In MP, 90 patients with CD and 131 patients with UC who responded to abatacept at week 12 in the induction trials were randomized to abatacept 10 mg/kg or placebo every 4 weeks through week 52. **RESULTS:** In CD-IP, 17.2%, 10.2%, and 15.5% of patients receiving abatacept 30, 10, and 3 mg/kg achieved a clinical response at weeks 8 and 12, vs 14.4% receiving placebo ($P = .611$, $P = .311$, and $P = .812$, respectively). In UC-IP1, 21.4%, 19.0%, and 20.3% of patients receiving abatacept 30, 10, and 3 mg/kg achieved a clinical response at week 12, vs 29.5% receiving placebo ($P = .124$, $P = .043$, and $P = .158$, respectively). In CD-MP, 23.8% vs 11.1% of abatacept vs placebo patients were in remission at week 52. In UC-MP, 12.5% vs 14.1% of patients receiving abatacept vs placebo were in remission at week 52. Safety generally was comparable between groups. **CONCLUSIONS: The studies showed that abatacept is not efficacious for the treatment of moderate-to-severe CD or UC.** ClinicalTrials.gov NCT00406653, NCT00410410.

Keywords: Clinical Trial; Inflammatory Bowel Disease; IBD; T-Cell Signaling Inhibitor.

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases.[1,2] Treatments either have broad mechanisms of action (mesalamine, corticosteroids, azathioprine, mercaptopurine, methotrexate) or target the tumor necrosis factor-α cytokine.[2] T cells are believed to play a role in the pathogenesis of both conditions; thus, therapies targeting T cells are of interest.[3]

T-cell activation requires co-stimulatory signaling via T cell CD28 and CD80 or CD86 on the antigen-presenting cell.[4] Naturally occurring inhibitory cytotoxic T-lymphocyte antigen 4 is induced on the T-cell surface 24–48 hours after activation and attenuates CD28-mediated costimulation. Cytotoxic T-lymphocyte antigen 4 has a greater affinity for CD80 or CD86 than CD28, and prevents CD28 binding to CD80 or CD86.[5] Abatacept is a recombinant fusion protein comprising a fragment of the Fc domain of human IgG1 and the extracellular domain of human cytotoxic T-lymphocyte antigen 4.[6] Similar to cytotoxic T-lymphocyte antigen 4, abatacept competes with CD28 for CD80 and CD86 binding to block costimulatory signaling, thus selectively modulating T-cell activation.[7] Abatacept is effective for rheumatoid arthritis[8,9] and juvenile idiopathic arthritis.[10] In animal models of colitis, abatacept reduces inflammation.[11,12]

We conducted 12-week induction trials of abatacept in patients with moderate-to-severe CD and UC. Responders enrolled in 52-week maintenance trials.

Materials and Methods

Patients

The initial CD and UC induction periods (CD-IP and UC-IP1) and maintenance periods (CD-MP and UC-MP) were randomized, double-blind, placebo-controlled studies conducted at 142 centers between December 2006 and November 2009. Protocols were approved by institutional review boards. Patients provided written informed consent.

Eligible patients were ≥18 years, with CD or UC (≥3 mo). Patients with CD had a Crohn's Disease Activity Index (CDAI) score[13] of 220–450 and a high sensitivity C-reactive protein concentration above the upper normal limit. Patients with UC had a Mayo Clinic score[14] of 6–12 with moderate-to-severely active disease on sigmoidoscopy (endoscopic subscore, ≥2). Patients had a current/previous inadequate response to, or did not

Abbreviations used in this paper: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CD-IP, Crohn's disease induction period; CD-MP, Crohn's disease maintenance period; SAE, serious adverse event; Treg, regulatory T cells; UC, ulcerative colitis; UC-IP, ulcerative colitis induction period; UC-MP, ulcerative colitis maintenance period.

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tolerate, ≥1: oral 5-aminosalicylates at or above the approved dose for ≥6 weeks (UC) or ≥8 weeks (CD); prednisone 40 mg/day for ≥2 weeks or intravenous hydrocortisone ≥400 mg/day for ≥1 week (UC) or ≥20 mg/day for ≥4 weeks or budesonide 9 mg/day for ≥4 weeks (CD); azathioprine ≥2 mg/kg body weight or 6-mercaptopurine ≥1 mg/kg body weight (or documented therapeutic concentration of 6-thioguanine nucleotide metabolite concentration) for ≥12 weeks; methotrexate ≥15 mg/week for ≥12 weeks (CD); or anti–tumor necrosis factor (approved dose) for ≥8 weeks. Concurrent therapies, including stable doses of oral 5-aminosalicylates, prednisolone (≤30 mg/day), budesonide (≤9 mg/day; CD), azathioprine, 6-mercaptopurine, methotrexate (CD), and antibiotics (CD) were permitted.

Excluded patients were those with previous proctocolectomy or subtotal colectomy with ileorectal anastomosis, those who needed bowel surgery, or had active tuberculosis within ≤3 years. Patients with symptomatic stricture, abscess, short-bowel syndrome, or without colonic or ileal involvement were excluded for CD; patients with proctitis were excluded for UC.

Study Design

The objective of these studies was to evaluate the induction and maintenance of response and remission in patients with moderate-to-severely active UC and CD.

In CD-IP and UC-IP1, patients randomly were assigned in a 1:2:2:2 ratio (CD) or a 2:2:1:2 ratio (UC) to intravenous abatacept (Orencia, Bristol-Myers Squibb, Princeton, NJ) at 30, 10, or 3 mg/kg, or placebo, dosed at weeks 0, 2, 4, and 8, and followed up through week 12. After enrollment of UC-IP1, a second UC induction period (UC-IP2) began enrolment, in which patients were assigned randomly in a 1:1 ratio to receive intravenous abatacept 10 or 30 mg/kg at weeks 0, 2, 4, and 8, and followed up through week 12. Patients receiving 30 mg/kg received 2 doses of 30 mg/kg followed by 2 doses of 10 mg/kg. In CD-MP and UC-MP, week 12 responders were assigned randomly (1:1) to intravenous abatacept (10 mg/kg) or placebo every 4 weeks through week 52. Randomization was performed centrally using dynamic treatment allocation.

In the CD-IP study, randomization was stratified by baseline disease (CDAI, <330 or ≥330) and concomitant use of azathioprine, 6-mercaptopurine, or methotrexate. In the UC-IP1 study, randomization was stratified by history of inadequate response or intolerance to infliximab. In the CD-MP study, randomization was stratified by disease activity after induction (CDAI, <150 or ≥150) and concomitant use of azathioprine, 6-mercaptopurine, or methotrexate. In the UC-MP study, randomization was stratified by concomitant use of corticosteroids, clinical remission (Mayo Clinic score ≤2 with no individual subscore >1) at week 12, and history of inadequate response or intolerance to infliximab.

Oral mesalamine, azathioprine, 6-mercaptopurine, methotrexate, and antibiotics were continued at stable doses during all studies. Prednisone and budesonide were continued at a stable dose during IP. During MP, tapering of corticosteroids was recommended, but not mandated, for patients in remission or with satisfactory improvement (at the investigator's based on clinical assessment).

Follow-Up Evaluation, Efficacy, and Safety

For CD, disease activity was assessed by CDAI, determined at weeks 0, 2, 4, and every 4 weeks thereafter.[15] Efficacy variables were as follows: response, reduction from baseline in CDAI score of ≥100 or absolute CDAI score of <150; remission, absolute CDAI of <150; and relapse: CDAI of ≥220 and an increase from week 12 of ≥100 for 2 consecutive visits. For UC, disease activity was assessed by the Mayo Clinic score, determined at weeks 0, 8, 12, 36, and 64.[16] Efficacy variables were as follows: response (reduction from baseline in Mayo Clinic score by ≥3 and ≥30%, with decrease in rectal bleeding subscore of ≥1, or absolute rectal bleeding subscore of 0 or 1); remission (Mayo Clinic score ≤2 with no individual subscore >1); and mucosal healing (absolute endoscopy score of 0 or 1). The partial Mayo Clinic score was determined at weeks 2, 4, 16, 20, 24, 28, 32, 40, 44, 48, and 52. Efficacy variables were as follows: response (reduction from baseline in partial Mayo Clinic score ≥2 and ≥30%, with decrease in rectal bleeding subscore of ≥1, or absolute rectal bleeding subscore of 0 or 1) and relapse (partial Mayo Clinic score of ≥4 and increase from week 12 of ≥2, and endoscopy subscore of 2 or 3).

Colon biopsy specimens were obtained in UC-IP1 and UC-MP at weeks 0, 8, 12, 36, and 52. Histologic disease activity was assessed by the Geboes[17] index. Immunohistochemistry was performed using a Dako automatic stainer with antibodies to CD68, CD20, CD86, CD4, FOXp3, caspase 3, and tenascin.

Adverse events and concomitant medications were followed up through 8 weeks after the last dose of study drug. Blood samples were collected for laboratory evaluations.

Statistical Analysis

The primary end point for CD-IP was CDAI response at both weeks 8 and 12; remission at these time points was a secondary end point. The primary end point for CD-MP was remission at week 52 of the MP. Secondary end points included response at week 52, remission at both weeks 24 and 52, and corticosteroid-free remission at week 52. The primary end point for UC-IP1 was the Mayo clinic score response at week 12. Secondary assessments included remission and mucosal healing at week 12. Efficacy results for UC-IP2 are not presented. The primary end point for UC-MP was response at week 52. Secondary end points included remission, mucosal healing, and corticosteroid-free remission at week 52, and remission at both weeks 24 and 52. Response, remission, and mucosal rates are presented with 95% confidence intervals and were compared for each abatacept treatment group vs placebo using the Cochran–Mantel–Haenszel chi-square tests, accounting for randomization stratification factors.

To control the overall type I error rate, all primary and key secondary end points in the CD-IP, UC-IP1, and UC-MP trials were tested in a prespecified sequential manner; accordingly, if prior comparisons were not significant (0.05 [2-sided] significance level for abatacept 30 mg/kg vs placebo), no subsequent comparisons were conducted. Because of the early termination of CD-MP and UC-MP, only descriptive statistics are presented.

To evaluate the consistency of treatment effect on response, subgroup analyses based on demographic or baseline disease characteristics were performed, as prespecified in the statistical analysis plan.

Efficacy and safety analyses included all randomized patients who received ≥1 dose of study medication. Patients who discontinued were considered not to have a response/remission. For the primary and key secondary end points of response and remission at both weeks 8 and 12, if a value was missing for reasons other than early discontinuation, the patient was excluded.

For the primary end point of response at weeks 8 and 12 in CD-IP, it was estimated that the abatacept 30-mg/kg and pla-

Table 1. Baseline Demographics and Disease Characteristics for Induction Period Studies

	Crohn's disease				Ulcerative colitis			
Characteristic	Abatacept 30/~10 mg/kg (n = 65)	Abatacept ~10 mg/kg (n = 128)	Abatacept 3 mg/kg (n = 130)	Placebo (n = 128)	Abatacept 30/~10 mg/kg (n = 141)	Abatacept ~10 mg/kg (n = 139)	Abatacept 3 mg/kg (n = 70)	Placebo (n = 140)
Mean age, y (SD)	36.0 (11.1)	38.6 (12.9)	36.9 (13.4)	38.0 (13.0)	43.4 (14.4)	42.1 (13.5)	40.4 (13.4)	40.9 (13.1)
Sex, % female	58.5	60.9	60.0	64.8	40.4	37.4	37.1	47.1
Mean weight, kg (SD)	72.2 (24.4)	72.0 (18.7)	74.5 (20.3)	72.2 (24.4)	73.2 (18.9)	74.4 (17.6)	73.6 (19.6)	74.4 (16.8)
Mean disease duration, y (SD)	8.4 (7.5)	9.9 (8.7)	9.2 (8.0)	9.8 (8.3)	6.3 (6.7)	7.0 (7.3)	5.4 (4.7)	6.6 (6.2)
Inadequate response/intolerance to prior therapy, %								
Oral aminosalicylates	75.4	78.9	73.1	71.9	89.4	87.8	94.3	89.3
Corticosteroids[a]	75.4	75.0	76.2	71.9	60.3	64.7	58.6	70.7
Immunosuppressants	83.1	75.8	83.1	81.3	53.9	60.4	62.9	59.3
Anti-TNF agent(s)	64.6	67.2	59.2	60.2	31.9	33.1	34.3	32.1
Mean hsCRP, mg/L (SD)	29.3 (40.4)	24.2 (28.8)	23.5 (23.3)	27.9 (33.0)	18.1 (40.2)	12.6 (24.3)	16.7 (36.7)	15.5 (37.1)
Immunosuppressant use, %	36.9	41.4	36.9	42.2	27.0	41.0	35.7	34.3
Prednisone use, %	36.9	38.3	33.1	34.4	41.8	41.7	38.6	44.3
Mean CDAI score (SD)	320.6 (61.6)	318.9 (65.1)	317.9 (59.9)	320.7 (72.1)	—	—	—	—
Mean Mayo score (SD)	—	—	—	—	8.9 (1.7)	8.8 (1.7)	8.6 (1.8)	8.8 (1.6)
Extent of disease, %								
Left-sided disease only	—	—	—	—	48.2	41.0	48.6	39.3
Extensive disease other	—	—	—	—	51.1	58.3	50.0	60.7

hsCRP, high sensitivity C-reactive protein; SD, standard deviation; TNF, tumor necrosis factor.
[a]Oral corticosteroids for Crohn's disease and oral or intravenous corticosteroids for ulcerative colitis.

cebo groups would require 134 patients each to provide 99% power to detect a difference of 30%, assuming a 55% response rate to abatacept 30 mg/kg and a 25% response rate to placebo. For the primary end point of response at week 12 in UC-IP1, it was estimated that the abatacept 30 mg/kg and placebo groups would require 140 patients each to provide 98% power to detect a difference of 25%, assuming a 65% response rate to abatacept 30 mg/kg and a 40% response rate to placebo.

Results

Patient Characteristics

For CD, 451 patients were randomized in CD-IP, with 90 randomized in CD-MP. For UC, 490 and 101 patients were randomized in UC-IP1 and UC-IP2, respectively, with 131 randomized in UC-MP. Patient disposition is shown (Supplementary Figure 1*A* and *B*). Because of early study termination, subsequent to analyses indicating lack of efficacy in CD-IP and UC-IP1, only 24 and 26 patients completed CD-MP and UC-MP, respectively. Therefore, secondary end points at week 52 were not analyzed. Baseline disease characteristics for CD-IP and UC-IP1 were similar between treatment groups (Tables 1 and 2).

Efficacy

Crohn's disease. Response at weeks 8 and 12 occurred in 17.2% of patients receiving abatacept 30 mg/kg (11 of 64), 10.2% receiving abatacept 10 mg/kg (13 of 128), and 15.5% receiving abatacept 3 mg/kg (20 of 129), vs 14.4% receiving placebo (18 of 125; $P = .611$, $P = .311$, and $P = .812$ for abatacept 30, 10, and 3 mg/kg vs placebo; Figure 1*A*). Remission rates at weeks 8 and 12 are shown in Figure 1*A*. Over the 12-week IP, there was no difference between groups in mean CDAI scores (Supplementary Figure 2).

Remission at week 52 of the MP occurred in 23.8% (10 of 42) of patients receiving abatacept vs 11.1% (5 of 45) of patients receiving placebo ($P = .082$). Response at week 52 of the MP occurred in 26.2% and 15.6% of patients receiving abatacept (11 of 42) and placebo (7 of 45), respectively ($P = .175$).

Ulcerative colitis. Response at week 12 occurred in 21.4% of patients receiving abatacept 30 mg/kg (30 of 140), 19.0% receiving 10 mg/kg (26 of 137), and 20.3% receiving 3 mg/kg (14 of 69) vs 29.5% receiving placebo (41 of 139; $P = .124$, $P = .043$, and $P = .158$ for abatacept 30, 10, and 3 mg, respectively, vs placebo). Remission rates at week 12 are shown in Figure 1*B*. Mucosal healing at week 12 occurred in 17.1% (24 of 140), 14.6% (20 of 137), and 15.9% (11 of 69) of patients receiving 30, 10, and 3 mg abatacept, respectively, vs 25.9% (36 of 139) receiving placebo. There was no difference between treatment groups in change from baseline in partial Mayo score over time (Supplementary Table 1).

Response at week 52 of the MP occurred in 17.2% of patients receiving abatacept (11 of 64) compared with 17.2% receiving placebo (11 of 64) ($P = .999$); clinical remission occurred in 12.5% (8 of 64) of patients receiving abatacept vs 14.1% (9 of 64) receiving placebo ($P = .740$).

Additional analyses. No consistent pattern was identified when assessing response rates during the IPs by concomitant immunomodulator use, prior therapy failure, disease duration, or baseline high sensitivity C-reactive protein in the subgroup analyses (Supplementary Figure 3). Changes from baseline to week 12 in high sensitivity C-reactive protein were comparable between groups (Supplementary Figure 4).

Safety

Crohn's disease. Safety generally was comparable across groups during the IP and MP (Table 2). During IP, frequencies of serious adverse events (SAEs) generally were

Table 2. Safety Summary From Crohn's Disease Studies

	Induction period				Maintenance period	
n (%)	Abatacept 30/~10 mg/kg (n = 65)	Abatacept ~10 mg/kg (n = 128)	Abatacept 3 mg/kg (n = 130)	Placebo (n = 128)	Abatacept ~10 mg/kg (n = 44)	Placebo (n = 46)
AEs	49 (75.4)	97 (75.8)	96 (73.8)	95 (74.2)	31 (70.5)	32 (69.6)
Related AEs	24 (36.9)	47 (36.7)	46 (35.4)	40 (31.3)	12 (27.3)	15 (32.6)
AEs leading to discontinuation	1 (1.5)	11 (8.6)	5 (3.8)	12 (9.4)	1 (2.3)	0
Deaths	0	0	0	0	0	0
SAEs	11 (16.9)	22 (17.2)	20 (15.4)	20 (15.6)	5 (11.4)	9 (19.6)
Related SAEs	2 (3.1)	7 (5.5)	9 (6.9)	6 (4.7)	0	1 (2.2)
Infections	13 (20.0)	33 (25.8)	31 (23.8)	42 (32.8)	16 (36.4)	18 (39.1)
Serious infections	2 (3.1)	9 (7.0)	4 (3.1)	3 (2.3)	1 (2.3)	1 (2.2)
Opportunistic infections	0	0	0	0	0	0
Malignancies	0	0	3 (2.3)	0	0	0
Possible autoimmune events	2 (3.1)	1 (0.8)	2 (1.5)	2 (1.6)	2 (4.5)	1 (2.2)
Acute infusional AEs	3 (4.6)	3 (2.3)	4 (3.1)	5 (3.9)	1 (2.3)	0

NOTE. The most common serious infection in the abatacept groups during the IP was anal abscess (n = 7); other serious infections were each reported in only 1 or 2 patients. No opportunistic infections were reported. Three malignancies occurred during the IP and MP periods (squamous cell carcinoma, 2; breast cancer, 1). The most common autoimmune event was erythema nodosum (6 events during the IP [abatacept 30/~10 mg/kg, 2; abatacept ~10 mg/kg, 1; abatacept 3 mg/kg, 2; placebo, 1] and one in the MP [placebo]).

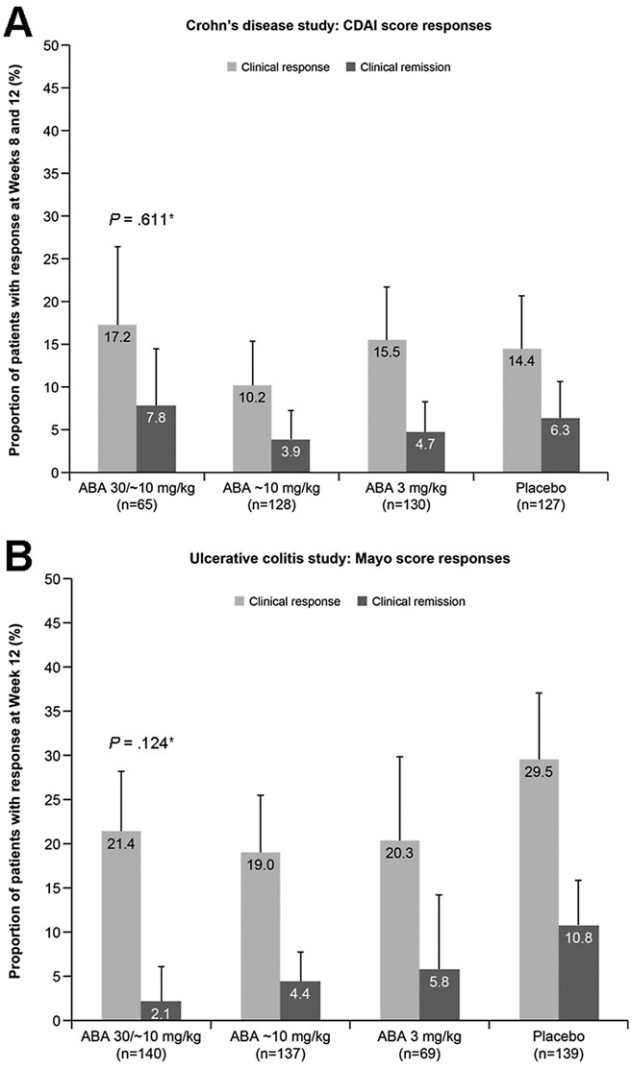

Figure 1. Response rates for the primary end points during the induction period. (*A*) CD-IP. Clinical response defined as a reduction from baseline in CDAI score by ≥100 points, or an absolute CDAI score <150 points. Remission was defined as an absolute CDAI score <150. (*B*) UC-IP1. Clinical response was defined as a reduction from baseline in Mayo score of ≥3 points and ≥30%, with decrease from baseline in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1. Remission was defined as a Mayo score ≤2 and no individual subscore >1 point. *Comparison with placebo using a Cochran–Mantel–Haenszel chi-square test controlling for randomization stratification factors. Based on a prespecified hierarchical comparison procedure, no formal testing of the primary end point for other treatment groups was conducted because abatacept 30/~10 mg/kg vs placebo was not statistically significant. *Error bars*, 95% CI.

comparable; during MP, a higher proportion of patients in the placebo group reported an SAE (19.6% vs 11.4%). During IP, serious infections were reported in 3.1%–7.0% of patients across the abatacept groups, and in 2.3% in the placebo group. During the MP, the frequencies of serious infections were comparable between treatment groups. No opportunistic infections were reported.

Ulcerative colitis. Safety generally was comparable across groups during the IP and MP (Table 3). One death occurred in the 30-mg/kg abatacept group during the IP (nosocomial pneumonia, septic shock, and acute respiratory failure) and 1 death occurred in the abatacept group during the MP (varicella, varicella pneumonia, and septicemia). In the IP, a numerically higher proportion of SAEs occurred with the abatacept groups vs placebo, driven by a higher rate of UC exacerbations in patients with severe UC (Mayo score, ≥10) at baseline (Supplementary Table 2). Of these patients with severe UC at baseline, the proportions requiring surgery during the IP for SAEs of UC exacerbation were 3.5%, 3.6%, 0%, and 0% for patients receiving 30, 10, or 3 mg/kg abatacept, or placebo, respectively. A numerically higher proportion of SAEs occurred with abatacept vs placebo during the MP, driven primarily by a higher frequency of serious infections (abatacept, 7.7%; placebo, 3.0%). Two opportunistic infections were reported during the IP, and 1 was reported in the MP.

Immunohistochemistry. Among the 52 patients in the biopsy substudy there was no significant difference in change in histologic grade over time across treatment groups (data not shown). The level of FOXp3 (marker for regulatory T cell) expression over time did not differ among biopsy specimens from abatacept-treated vs placebo-treated patients, or across abatacept treatment groups (Supplementary Figure 5). There was no correlation between the level of expression of CD86 (marker for antigen-presenting cell) at baseline, and duration of disease (data not shown).

Discussion

These results show that abatacept is not effective in patients who have moderate-to-severe CD or UC. In patients with severe UC (Mayo score, ≥10), there were numerically higher rates of disease exacerbation and colectomy among patients treated with abatacept. There was no evidence of efficacy in any patient subgroups including concomitant immunomodulator use, disease duration, high sensitivity C-reactive protein and type of, or reason for, prior treatment failure. A potential limitation of these studies was that colonoscopy/sigmoidoscopy was not performed to confirm active disease at enrollment in the CD study, and data were not collected during treatment in the study. Such assessments were not common practice when these trials were designed.

A hallmark of the immunopathology of active UC and CD is infiltration of innate and adaptive immune cells into the lamina propria. Increased numbers and activation of these cells increase concentrations of proinflammatory cytokines in the mucosa, including tumor necrosis factor-α, interleukin-1β, interleukin-6, and interferon-γ. Tumor necrosis factor antagonists have shown efficacy in both CD and UC, and other therapies that modulate cytokines currently are being actively tested. Over the past decade, therapies targeting T-cell activation have been investigated. Cyclosporine and tacrolimus are effective for induction of response in hospitalized patients with intravenous steroid-refractory UC.[18,19] However, it is questionable whether the biologic effects of these calcineurin in-

Table 3. Safety Summary From Ulcerative Colitis Studies

	Induction period 1				Induction period 2		Maintenance period	
n (%)	Abatacept 30/~10 mg/kg (n = 141)	Abatacept ~10 mg/kg (n = 139)	Abatacept 3 mg/kg (n = 70)	Placebo (n = 140)	Abatacept 30/~10 mg/kg (n = 51)	Abatacept ~10 mg/kg (n = 50)	Abatacept ~10 mg/kg (n = 65)	Placebo (n = 66)
AEs	85 (60.3)	92 (66.2)	39 (55.7)	86 (61.4)	26 (51.0)	27 (54.0)	39 (60.0)	36 (54.5)
Related AEs	48 (34.0)	46 (33.1)	23 (32.9)	37 (26.4)	10 (19.6)	11 (22.0)	12 (18.5)	13 (19.7)
Deaths	1 (0.7)	0	0	0	0	0	1 (1.5)	0
AEs leading to discontinuation	4 (2.8)	6 (4.3)	2 (2.9)	5 (3.6)	1 (2.0)	0	1 (1.5)	3 (4.5)
SAEs	22 (15.6)	20 (14.4)	8 (11.4)	7 (5.0)	6 (11.8)	4 (8.0)	7 (10.8)	4 (6.1)
Related SAEs	4 (2.8)	1 (0.7)	1 (1.4)	3 (2.1)	1 (2.0)	0	2 (3.1)	2 (3.0)
SAE—UC exacerbations	13 (9.2)	16 (11.5)	5 (7.1)	4 (2.9)	5 (9.8)	4 (8.0)	3 (4.6)	1 (1.5)
Infections	23 (16.3)	29 (20.9)	8 (11.4)	25 (17.9)	12 (23.5)	7 (14.0)	39 (60.0)	36 (54.4)
Serious infections	5 (3.5)	0	1 (1.4)	0	0	0	5 (7.7)	2 (3.0)
Opportunistic infections	0	1 (0.7)	1 (1.4)	0	0	0	1 (1.5)	0
Malignancies	1 (0.7)	0	0	1 (0.7)	0	0	0	1 (1.5)
Possible autoimmune events	2 (1.4)	1 (0.7)	0	4 (2.9)	0	0	2 (3.1)	0
Acute infusional AEs	4 (2.8)	4 (2.9)	0	2 (1.4)	0	0	2 (3.1)	1 (1.5)

NOTE. A higher rate of infection was observed in both groups during the MP compared with the IP. Two opportunistic infections were reported during the IP (candidiasis [~10 mg/day], esophageal candidiasis [3 mg/day]), and 1 infection in the MP (varicella pneumonia [~10 mg/day]). Three malignancies were reported during the IP and MP periods (abatacept 30/~10 mg/day, basal cell carcinoma; placebo, malignant melanoma and breast cancer); the case of basal cell carcinoma was considered unrelated to the study drug. The frequency of autoimmune events and acute infusional AEs was low during both the IP and MP, and rates were similar across groups.

hibitors are limited to T-cell activation. Conversely, more specific T-cell therapies such as visilizumab (anti-CD3),[20] daclizumab,[21] and basiliximab (anti-CD25)[22] failed to show efficacy in UC. Abatacept modulates T-cell function by inhibiting the co-stimulatory signal required for full naive T-cell activation. In aggregate, these findings suggest that T-cell modulation alone may not be effective for treatment of UC, and likely CD as well.

The balance between effector and $CD4^+$ $Foxp3^+$ regulatory T cells (Tregs) is critical for maintaining immune homeostasis in the colon. Although a decrease of Treg numbers and increase of proinflammatory Th17 cells has been observed in the peripheral blood of inflammatory bowel disease patients,[23] an increase in numbers of Tregs has been seen in the lamina propria and mesenteric lymph nodes.[24–26] A recent study found that Foxp3 was highly expressed in the intestinal mucosa of both UC and CD patients, suggesting that Tregs actively were being recruited to suppress ongoing active inflammation.[23] Whether these Tregs have a suppressor activity and/or they are on their way to be converted to Th17 cells by prolonged exposure to inflammatory cytokines, such as interleukin-1β and interleukin-6, is unknown.[27] We assessed whether decreased Tregs in colonic tissue potentially could explain the lack of efficacy observed in these studies by performing immunohistochemistry staining for Foxp3 expression in colonic biopsy specimens. Treatment with abatacept did not change the number of Foxp3 Tregs in colonic tissue. Whether or not these cells still had suppressive activity was not determined, but in vitro studies have suggested that abatacept does not impact Treg function (data not shown).

It has been suggested that dysregulation of T-cell activation may play a significant role early in the disease process in which an innate immune response to antigens from commensal flora leads to an increase in cytokines produced by CD4 T cells. Our data suggest that in more established disease, additional factors (such as disruption of intestinal epithelia barrier function and inflammatory mediators leading to recruitment of leukocytes) likely create a hurdle that cannot be overcome by blocking T-cell activation alone.

In trinitrobenzene sulfonic acid and oxazalone murine colitis models, prophylactic treatment with abatacept showed efficacy as measured by prevention of weight loss, reduction in proinflammatory cytokine production, and reduction in mucosal damage.[28,29] However, in the same murine model, abatacept failed to induce remission in established colitis, once again suggesting that targeting T-cell activation alone may not be efficacious in established disease.

In conclusion, these studies showed that abatacept is not efficacious for the treatment of moderate-to-severe CD or UC.

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.

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Conflicts of interest

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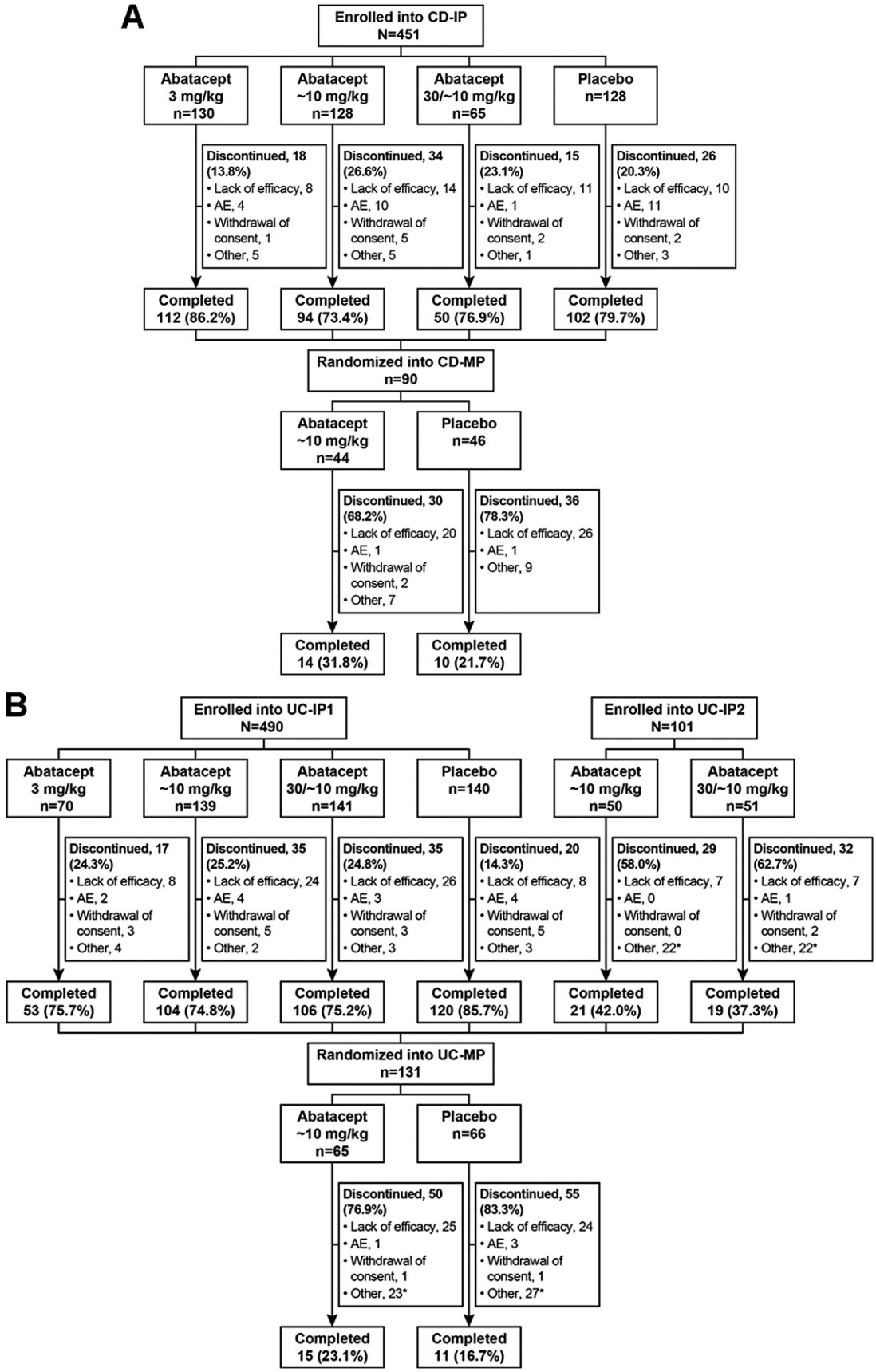
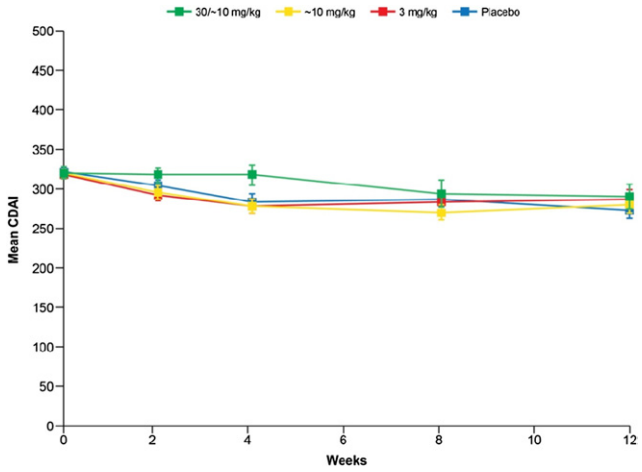


Supplementary Figure 1. Patient disposition. (*A*) Crohn's disease study; (*B*) ulcerative colitis study. *Includes administrative reason by sponsor.

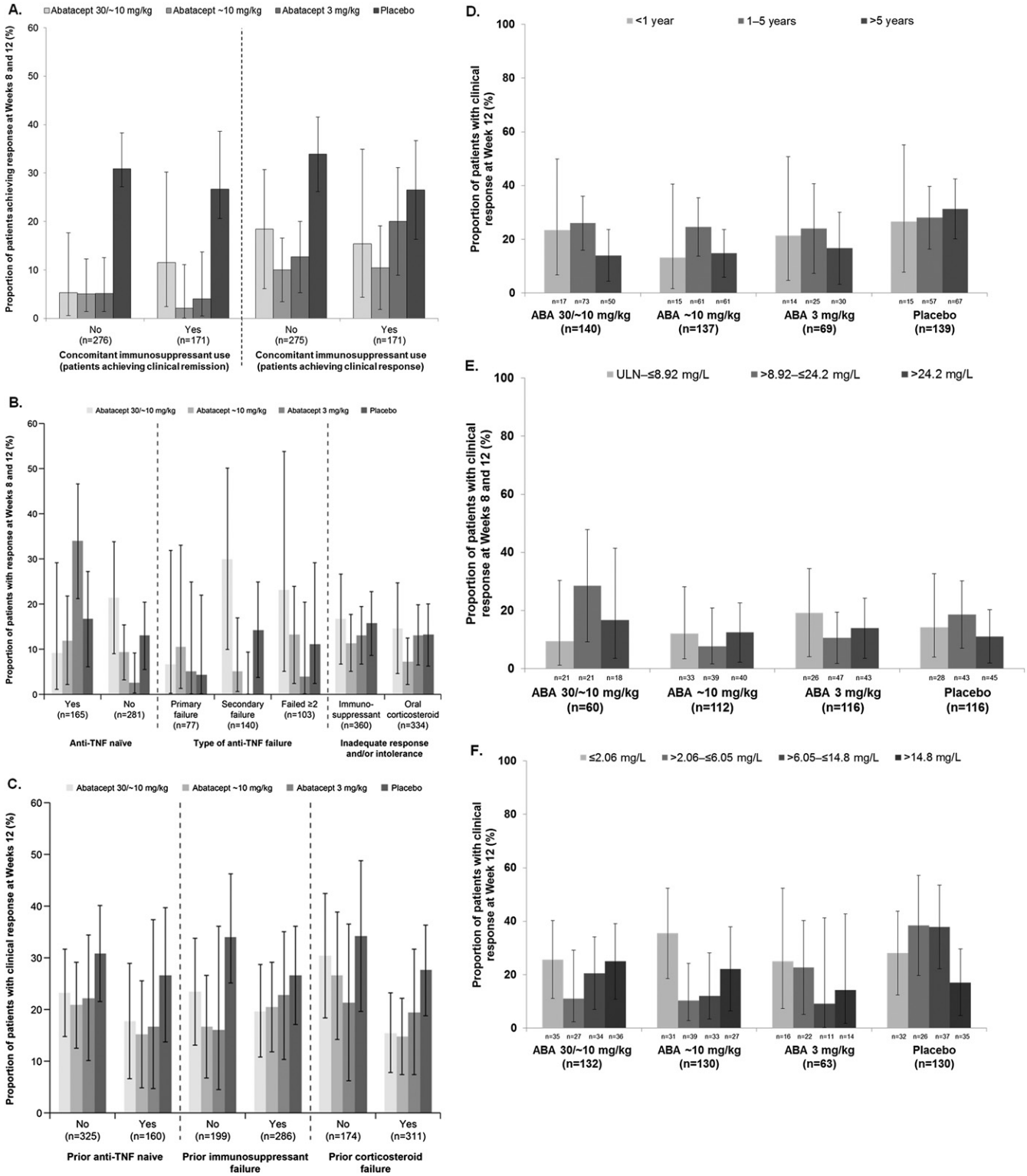


Supplementary Figure 2. CDAI scores over time in the IP group in the Crohn's disease study. Error bars represent the standard error of the mean.

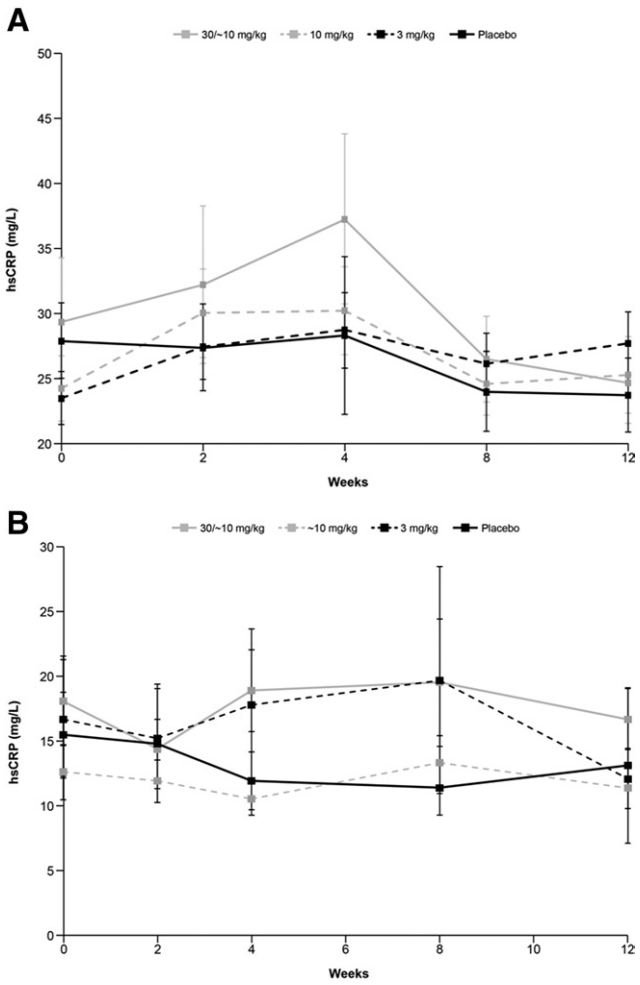
Supplementary Table 1. Partial Mayo Score Over Time in the Induction Period Study in Ulcerative Colitis

	Abatacept 30/~10 mg/kg (n = 140)	Abatacept ~10 mg/kg (n = 137)	Abatacept 3 mg/kg (n = 69)	Placebo (n = 139)
Baseline				
Mean	6.3 (1.5)	6.2 (1.5)	6.1 (1.6)	6.2 (1.4)
Week 2				
Mean	5.4 (2.0)	5.3 (2.1)	5.0 (2.1)	5.2 (1.9)
Mean change from baseline	−0.9 (−1.2 to −0.6)	−0.9 (−1.2 to −0.7)	−0.9 (−1.3 to −0.6)	−0.9 (−1.2 to −0.7)
Week 4				
Mean	5.3 (2.1)	5.1 (2.3)	4.9 (2.6)	5.0 (2.0)
Mean change from baseline	−0.9 (−1.2 to −0.5)	−1.1 (−1.4 to −0.8)	−1.0 (−1.6 to −0.5)	−1.2 (−1.5 to −0.9)
Week 8				
Mean	5.5 (2.5)	5.2 (2.1)	5.3 (2.2)	4.9 (2.3)
Mean change from baseline	−0.7 (−1.0 to −0.3)	−1.0 (1.4 to −0.7)	−0.6 (−1.2 to −0.0)	−1.3 (−1.7 to −0.9)
Week 12				
Mean	5.5 (2.1)	5.2 (2.2)	5.3 (2.4)	4.7 (2.5)
Mean change from baseline	−0.8 (−1.1 to −0.4)	−1.0 (−1.3 to −0.6)	−0.6 (−1.2 to 0.0)	−1.4 (−1.8 to −1.1)

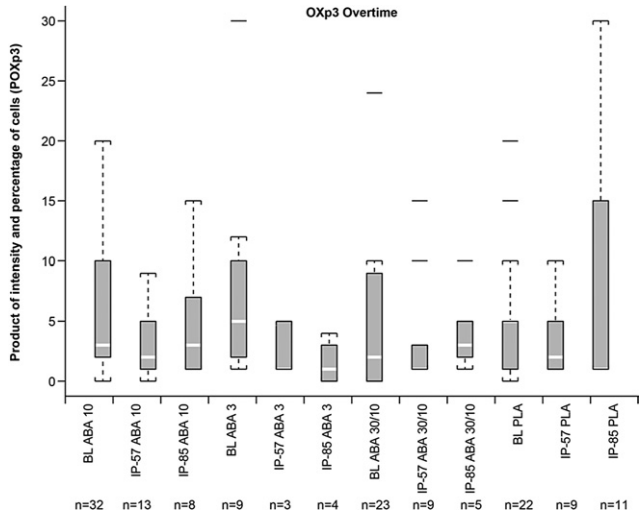
NOTE. Data are presented for IP and do not include data for the IP2 group. Data are means (standard deviations) and mean change from baseline (95% confidence intervals).



Supplementary Figure 3. Subgroup analyses for the rate of primary clinical responses during the induction period. *(A)* Response at weeks 8 and 12 by concomitant immunosuppressant use (CD). *(B)* Response at weeks 8 and 12 by prior therapy (CD). *(C)* Response at week 12 by prior therapy (UC). *(D)* Response at week 12 by disease duration (UC). *(E)* Response at weeks 8 and 12 by baseline high sensitivity C-reactive protein (hsCRP) (CD). Patient numbers for subgroups were not consistent with other analyses because some patients had CRP values greater than the upper limit of normal (ULN) at screening but not randomization. *(F)* Response at week 12 by baseline hsCRP (UC). Clinical response was defined as a reduction from baseline in CDAI score by ≥100 points, or an absolute CDAI score <150 points for the CD study, and a reduction from baseline in the Mayo score of ≥3 points and ≥30%, with a decrease from baseline in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 for the UC study. Error bars, 95% confidence interval (CI); TNF, tumor necrosis factor.



Supplementary Figure 4. High sensitivity C-reactive protein (hsCRP) concentrations over time during the IP. (*A*) Crohn's disease; (*B*) ulcerative colitis. Error bars represent the standard error of the mean.



Supplementary Figure 5. FOXp3 expression shown as the product of intensity and percentage of positive cells at day 1, month 2, and month 3 in the induction period study in ulcerative colitis, in the individual abatacept treatment groups. White bars, median; box, range of 25% to 75% (mid 2 quartiles); whiskers, the farthest observation within the 1.5× the range of the middle 2 quartiles. Colon biopsy specimens were obtained in UC-IP1 and UC-MP at weeks 0, 8, 12, 36, and 52. Formalin-fixed samples were analyzed by a central pathologist in a blinded fashion. Histologic disease activity was determined according to the Geboes index.[17] Immunohistochemistry was performed using a Dako automatic stainer with antibodies to CD68, CD20, CD86, CD4, FOXp3, caspase 3, and tenascin. The intensity of the staining and the percentage of positive cells as a mean of 5 random high-power fields in the lamina propria were determined. ABA 10, abatacept ~10 mg/kg; ABA3, abatacept 3 mg/kg; ABA 30/10, abatacept 30/~10 mg/kg; BL, baseline; IP-57, induction period day 57; IP-85, induction period day 85; PLA, placebo.

Supplementary Table 2. Serious Adverse Events of Ulcerative Colitis Exacerbation in the Induction Period Study in Ulcerative Colitis

n (%)	Abatacept 30/~10 mg/kg (n = 141)	Abatacept ~10 mg/kg (n = 139)	Abatacept 3 mg/kg (n = 70)	Placebo (n = 140)
SAE of UC exacerbation	13 (9.2)	16 (11.5)	5 (7.1)	4 (2.9)
Patients with moderate UC at baseline	4 (2.8)	7 (5.0)	2 (2.9)	3 (2.1)
Patients with severe UC at baseline	9 (6.4)	9 (6.5)	3 (4.3)	1 (0.7)
SAE of UC exacerbation requiring surgery	7 (5.0)	7 (5.0)	2 (2.9)	1 (0.7)
Patients with moderate UC at baseline	2 (1.4)	2 (1.4)	2 (2.9)	1 (0.7)
Patients with moderate UC at baseline	5 (3.5)	5 (3.6)	0	0

NOTE. Moderate UC was defined as a Mayo score of 6–9; severe UC was defined as a Mayo score of ≥10.