Adalimumab for Maintenance of Clinical Response and Remission in Patients With Crohn's Disease: The CHARM Trial

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Background & Aims: **This study evaluated the efficacy and safety of adalimumab, a fully human, anti–tumor necrosis factor monoclonal antibody administered subcutaneously, in the maintenance of response and remission in patients with moderate to severe Crohn's disease (CD).** ***Methods:*** **Patients received open-label induction therapy with adalimumab 80 mg (week 0) followed by 40 mg (week 2). At week 4, patients were stratified by response (decrease in Crohn's Disease Activity Index ≥70 points from baseline) and randomized to double-blind treatment with placebo, adalimumab 40 mg every other week (eow), or adalimumab 40 mg weekly through week 56. Coprimary end points were the percentages of randomized responders who achieved clinical remission (Crohn's Disease Activity Index score <150) at weeks 26 and 56.** ***Results:*** **The percentage of randomized responders in remission was significantly greater in the adalimumab 40-mg eow and 40-mg weekly groups versus placebo at week 26 (40%, 47%, and 17%, respectively; $P < .001$) and week 56 (36%, 41%, and 12%, respectively; $P < .001$). No significant differences in efficacy between adalimumab eow and weekly were observed. More patients receiving placebo discontinued treatment because of an adverse event (13.4%) than those receiving adalimumab (6.9% and 4.7% in the 40-mg eow and 40-mg weekly groups, respectively).** ***Conclusions:*** **Among patients who responded to adalimumab, both adalimumab eow and weekly were significantly more effective than placebo in maintaining remission in moderate to severe CD through 56 weeks. Adalimumab was well-tolerated, with a safety profile consistent with previous experience with the drug.**

Tumor necrosis factor (TNF) is an important cytokine in the pathogenesis of Crohn's disease (CD), with elevated concentrations playing a role in pathologic inflammation.[1,2] Clinical trials have demonstrated the efficacy of infliximab, a chimeric monoclonal antibody to TNF, for induction and maintenance therapy of patients with moderate to severe CD, including those with draining fistulas.[3–7] Infusions of infliximab, especially when given episodically, may result in the development of antibodies to infliximab, which in turn may lead to infusion reactions, loss of efficacy, and delayed hypersensitivity reactions.[8–12]

Adalimumab (Humira; Abbott Laboratories, Abbott Park, IL) is a subcutaneously administered, recombinant, fully human, immunoglobulin G1 monoclonal antibody that binds with high affinity and specificity to human TNF, but not lymphotoxin, and modulates biologic responses induced or regulated by TNF. Controlled trials have demonstrated the efficacy of adalimumab in the treatment of patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis (all 3 Food and Drug Administration–approved indications)[13–21] as well as in psoriasis.[22–24]

Previously, a phase 3, 4-week, placebo-controlled induction trial, Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease (CLASSIC I), demonstrated that an adalimumab loading-dose regimen of 160 mg given subcutaneously at week 0 and 80 mg given subcutaneously at week 2 was significantly more effective than placebo in inducing remission in 299 patients with moderate to severe CD who were naive to TNF-antagonist therapy (36% vs 12%, $P = .001$).[25] More recently, CLASSIC II, a small, phase 2,

Abbreviations used in this paper: CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; TNF, tumor necrosis factor.

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randomized, placebo-controlled, maintenance follow-up trial to CLASSIC I, demonstrated that adalimumab 40 mg subcutaneously every other week or weekly was superior to placebo in maintaining remission over a 56-week period in 55 patients with moderate to severe CD naive to TNF-antagonist therapy who experienced remission with adalimumab induction therapy.[26]

In this report, we describe the Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM). CHARM was a large, phase 3, randomized, double-blind, placebo-controlled, 56-week study conducted in patients with moderate to severe CD who may or may not have previously received TNF-antagonist therapy. The findings presented here address the primary objective of the study, which was to assess the benefit of 2 adalimumab dosing regimens in maintaining clinical remission at 26 and 56 weeks in patients who had an initial response to 2 adalimumab injections of 80 mg at week 0 and 40 mg at week 2.

Materials and Methods

Patients

CHARM included men and women 18–75 years of age with known CD of at least 4 months' duration (radiologic/endoscopic confirmation required) that at the screening visits was moderately to severely active, as defined by a baseline Crohn's Disease Activity Index (CDAI) score of 220–450 points. Concurrent therapies for CD, including stable dosages (for at least 4 weeks before screening) of azathioprine, 6-mercaptopurine, methotrexate, 5-aminosalicylates, sulfasalazine, oral mesalamine, and CD-related antibiotics, were permitted, as were stable dosages (for at least 2 weeks before screening) of prednisone (≤30 mg/day or equivalent) or budesonide (≤9 mg/day) (patients could not be on both prednisone and budesonide). Patients who had received infliximab or any TNF antagonist other than adalimumab more than 12 weeks before screening could be enrolled provided that they did not exhibit initial nonresponse to the agent (ie, no clinical response to first injection as judged by the investigator). Female patients of childbearing potential were required to use an effective form of birth control.

Patients were excluded if they had ulcerative colitis, symptomatic obstructive disease, bowel resection within the past 6 months, an ostomy, extensive small bowel resection (as determined by the investigator), or short bowel syndrome; were currently receiving total parenteral nutrition; had a history of cancer, *Listeria*, human immunodeficiency virus, central nervous system demyelinating disease, or untreated tuberculosis; had received investigational chemical agents within 30 days or investigational biologic therapy within 3 months before screening; had received antibiotic treatment for non-CD–related infections within 3 weeks before screening; were pregnant or breast-feeding; had a history of significant drug or alcohol abuse within the past year; had poorly controlled medical conditions; had received treatment with adalimumab or participated in an adalimumab clinical study; had received enema therapy within 2 weeks before screening; had received cyclosporine, mycophenolate mofetil, or tacrolimus within 8 weeks of screening; had a positive *Clostridium difficile* stool assay; or had clinically significant deviations in prespecified laboratory parameters.

Study Design

This was a randomized, double-blind, placebo-controlled, multicenter efficacy and safety study conducted at 92 sites in Europe, the United States, Canada, Australia, and South Africa from July 2003 to September 2005. The institutional review board or independent ethics committee at each participating site approved the protocol, and written informed consent was obtained from all patients.

Patients entered a 2-week screening period before their baseline assessments. At the baseline visit (week 0), all eligible patients received open-label adalimumab 80 mg subcutaneously followed by a 40-mg dose at week 2. At week 4, patients were randomized to one of 3 treatment groups (adalimumab 40 mg every other week, adalimumab 40 mg weekly, or placebo) and continued treatment through week 56. Also at week 4, patients were stratified by responder status (ie, whether or not they attained a decrease in CDAI of ≥70 points compared with baseline) and previous exposure to TNF antagonists. All patients were randomized centrally using an interactive voice response system. Patients, study coordinators, and study investigators were blinded to treatment assignment throughout the blinded portion of the study.

After randomization, patients experiencing a disease flare (increase in CDAI of ≥70 points compared with week 4 and a CDAI score >220) or sustained nonresponse (did not attain a CDAI decrease of ≥70 points compared with baseline) at or after week 12 were switched to open-label treatment with 40 mg adalimumab every other week. This dosage could be escalated to open-label treatment with 40 mg weekly for those with continued nonresponse or recurrent flare. Continued nonresponse with the open-label 40-mg weekly dosage resulted in withdrawal from the study.

At week 8, patients receiving corticosteroids who experienced a significant improvement in CD symptoms (decrease in CDAI of ≥70 points compared with baseline) could begin reducing their corticosteroid dosages. If a patient experienced a loss of clinical response (decrease in CDAI became <70 points lower than baseline on 2 consecutive visits), the dosage of prednisone or budesonide could be increased back to the dosage used at the beginning of the study.

The coprimary efficacy end points were the percentage of week-4 responders (defined as a decrease in CDAI scores ≥70 points at week 4 compared with baseline:

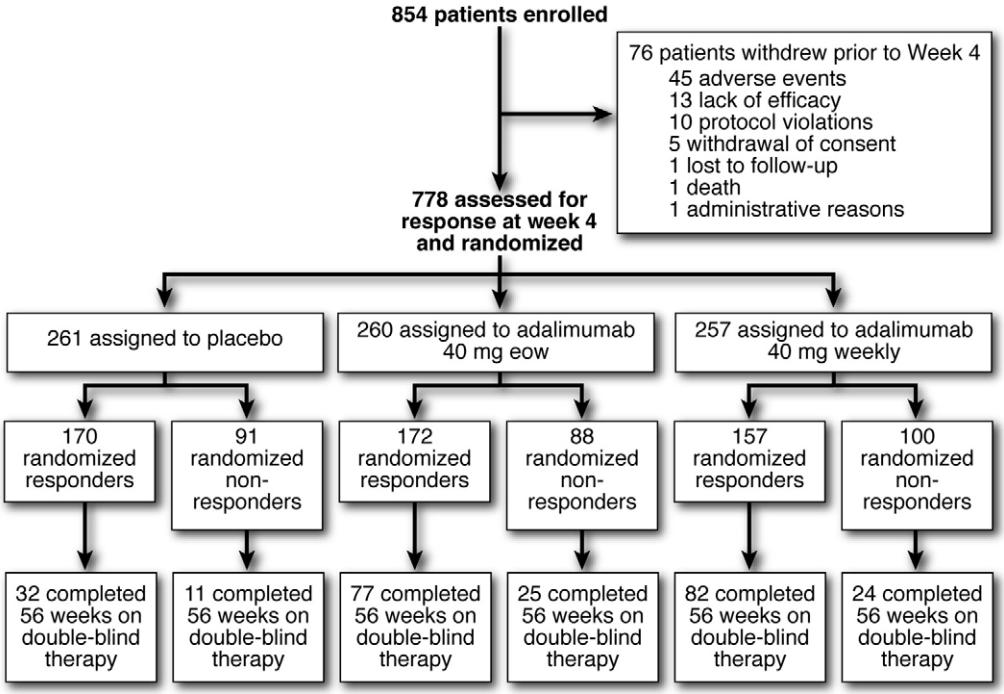

Figure 1. Trial profile. eow, every other week.

"randomized responders") who achieved clinical remission (CDAI score <150) at weeks 26 and 56. Prespecified secondary end points and subgroup analyses included (1) percentage of patients with a clinical response (decrease in CDAI score from baseline by ≥70 points and by ≥100 points) at weeks 26 and 56; (2) changes from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) total scores at weeks 26 and 56; (3) percentage of patients in clinical remission at weeks 26 and 56 who were able to discontinue corticosteroid use; (4) percentage of patients in clinical remission at weeks 26 and 56 who were able to discontinue corticosteroid use for ≥90 days; (5) percentage of patients with fistula remission (closure of all fistulas that were draining at screening and baseline visits); (6) previous/concomitant use of immunosuppressants (with vs without), and previous use of TNF antagonists (experienced vs naive); and (7) median time in clinical remission among randomized responders achieving remission. Post-hoc analyses were conducted to evaluate the sustainability of response and the response in certain subgroups. These included (1) percentage of patients with fistula closure at 26 weeks who continued to have fistula closure at 56 weeks and (2) clinical remission rates stratified by baseline C-reactive protein (CRP) concentration (<1 vs ≥1 mg/dL).

Efficacy and Safety Evaluations

Patients were assessed at weeks 0, 2, 4, 6, 8, 12, 16, 20, 26, 32, 40, 48, 56, and 60 (end of 4-week follow-up period). At each visit, the CDAI score was calculated, CRP concentration and the number of cutaneous fistulas draining upon gentle compression were assessed, adverse events and concomitant medications were recorded, and the following safety assessments were performed: vital signs, physical examination, hematologic analysis, serum biochemistry analysis, and urinalysis. The IBDQ was administered to assess patient-reported outcomes at weeks 0, 4, 12, 26, and 56.

Statistical Analysis

We estimated that 160 patients per treatment arm (total of 480 patients for primary analysis of week-4 responders) would provide a statistical power of 87% at a 0.05 α-level and 80% at an adjusted 0.025 α-level to detect a 14% absolute difference in clinical remission rates between adalimumab and placebo groups, assuming a 14% clinical remission rate in the placebo arm and a 28% remission rate in the adalimumab arms at week 56. This would also provide >90% power to test clinical remission rate at week 26. With an assumed 58% of patients achieving clinical response at week 4, approximately 830 patients were required at study baseline to allow 160 patients to be equally allocated to the 3 treatment arms at week 4.

The primary efficacy end point analysis was performed on the randomized responder population, which included all treated patients who achieved clinical response (decrease in CDAI of ≥70 points) at week 4 and were randomized to receive one of 3 blinded treatments. Patients who switched to open-label therapy or who withdrew from the study altogether were counted as remission failures. Secondary efficacy analyses were conducted

Table 1. Baseline Demographics and Clinical Characteristics

Characteristic	All patients (N = 854)	Week-4 randomized responders[a] (n = 499)	Week-4 randomized nonresponders[a] (n = 279)	Nonrandomized (week 4 withdrawals)[a] (n = 76)
Male patients, n (%)	326 (38.2)	188 (37.7)	108 (38.7)	30 (39.5)
Age (*y*), mean (SD)	37.1 (11.9)	36.7 (11.6)	37.9 (11.8)	36.1 (13.6)
Body wt (*kg*), mean (SD)	70.5 (17.8)	70.2 (17.8)	72.1 (18.0)	67.1 (15.9)
Involved intestinal area, n (%)[b]				
Colonic	640 (74.9)	375 (75.2)	206 (73.8)	59 (77.6)
Ileal	621 (72.7)	357 (71.5)	214 (76.7)	50 (65.8)
Gastroduodenal	43 (5.0)	30 (6.0)	10 (3.6)	3 (3.9)
Other	129 (15.1)	68 (13.6)	44 (15.8)	17 (22.4)
Enterocutaneous or perianal fistula at both screening and baseline, n (%)	130 (15.2)	64 (12.8)	53 (19.0)	13 (17.1)
Baseline CDAI score, mean (SD)	313.1 (62.0)[c]	316.6 (62.5)	301.6 (56.4)	333.3 (70.8)
IBDQ, median (range)[d]	122.0 (44–205)	125.0 (44–196)	120.0 (55–197)	112.5 (27.7)
CRP (*mg/dL*)				
Mean (SD)	2.3 (3.4)	2.4 (3.7)	1.8 (2.2)	3.6 (4.1)
Median (range)	0.9 (0.02–35.0)	0.9 (0.02–35.0)	0.9 (0.02–12.3)	1.89 (0.03–18.8)
CRP concentration ≥1.0 mg/dL (10 mg/L), n (%)	407 (47.7)	236 (47.3)	126 (45.2)	45 (59.2)
Previous TNF-antagonist exposure, n (%)	424 (49.6)	238 (47.7)	152 (54.5)	34 (44.7)
Concomitant medication, n (%)				
Any corticosteroid[e]	376 (44.0)	210 (42.1)	129 (46.2)	37 (48.7)
Prednisone	244 (28.6)	130 (26.1)	86 (30.8)	26 (34.2)
Budesonide	100 (11.7)	48 (9.6)	39 (14.0)	13 (17.1)
Any immunosuppressive agent	399 (46.7)	240 (48.1)	126 (45.2)	33 (43.4)
Azathioprine	275 (32.2)	165 (33.1)	88 (31.5)	19 (25.0)
6-Mercaptopurine	81 (9.5)	38 (7.6)	27 (9.7)	14 (18.4)
Methotrexate	90 (10.5)	49 (9.8)	29 (10.4)	9 (11.8)
5-aminosalicylates[f]	334 (39.1)	206 (41.3)	100 (35.8)	28 (36.8)
Current smoker, n (%)	303 (35.5)	176 (35.3)	101 (36.2)	26 (34.2)

[a]Among the patients randomized at week 4, there were no statistically significant differences between randomized responders and randomized nonresponders. CDAI and CRP values were statistically significantly greater for the patients randomized at week 4 versus the 76 patients who withdrew before week 4 randomization.
[b]Patient could have had multiple CD locations.
[c]One unrandomized patient did not have a baseline CDAI score.
[d]Scores for the IBDQ can range from 32 to 224; higher scores indicate a better quality of life.
[e]Includes betamethasone, budesonide, dexamethasone, deflazacort, cortisone, cloprednol, fluocortolone, glucocorticoids, glucocorticosteroids, hydrocortisone, methylprednisolone, prednisolone, prednisone, paramethasone, and prednylidene.
[f]Aminosalicylic acid, balsalazine, mesalazine, olsalazine, sulfasalazine.

for all treated patients, including both the randomized responder and randomized nonresponder groups (all randomized patients who failed to achieve a clinical response at week 4). Secondary efficacy results presented here describe comparisons between both adalimumab dosage groups and the placebo group using the randomized responder population to support the primary efficacy analysis. Fistula results were evaluated among all randomized patients with draining fistulas at baseline and screening visits (both the randomized responders and the randomized nonresponders). According to the prespecified analysis plan, fistula data from both adalimumab dosing groups (every other week and weekly) were combined and compared with patients receiving placebo. The population for safety analyses consisted of all patients who received at least one dose of study medication.

All analyses used 2-sided tests with an α-level of 0.05. For the primary efficacy analysis, the Cochran–Mantel–Haenszel χ^2 test adjusting for previous TNF-antagonist use was used to compare the percentage of week-4 responders in clinical remission at weeks 26 and 56 between each adalimumab arm and the placebo treatment group. Patients without CDAI assessments at weeks 26 or 56 were classified as remission failures.

For secondary efficacy analyses in the randomized responder population, continuous variables were compared using analysis of covariance adjusted for baseline value. Discrete variables were compared using the χ^2 test. The numbers and percentages of patients experiencing adverse events were to be tabulated by body system and Medical Dictionary for Drug Regulatory Affairs–preferred terms. Investigators could report exacerbations of CD as adverse events (mandated by the Food and Drug

Administration). However, reporting of CD as an adverse event was independent of qualifying a patient as a remission failure or experiencing a disease flare. Patients who met the protocol definition of flare (increase in CDAI of ≥70 points vs week 4 and total CDAI score >220) were switched out of the randomized treatment arm to open-label therapy. Once in open-label therapy, additional flares led to dosage escalation to weekly treatment. Adverse event results were summarized and reported by randomized treatment group.

Role of the Funding Source

This study was designed by selected study investigators (including J.-F.C., W.J.S., P.R., and S.B.H.) and staff members from Abbott Laboratories. Selected investigators and Abbott Laboratories' staff members, including those who designed the study and analyzed and interpreted the data, wrote this manuscript and agreed to submit it for publication. The principal investigator (J.-F.C.) approved the content of the report before submission.

Results

Patient Disposition and Baseline Characteristics

A total of 854 patients enrolled in the trial and received induction therapy with 80 mg of adalimumab at week 0 and 40 mg of adalimumab at week 2 (Figure 1). Of these, 76 withdrew before randomization at week 4. The most common reasons for study discontinuation were adverse events and lack of efficacy. The remaining 778 patients were randomized at week 4 to receive placebo (n = 261), adalimumab 40 mg every other week (n = 260), or adalimumab 40 mg weekly (n = 257). A total of 505 enrolled patients (59%) completed the 56-week study. Of these, 251 patients (50%) remained on their randomized, double-blind treatments, whereas 123 completed the study on open-label adalimumab 40 mg every other week and 140 completed the study on open-label adalimumab 40 mg weekly. Nine additional patients discontinued the study before week 56 but were included in the week-56 analysis by virtue of results imputed from their last visits (because these visits fell within the protocol parameters of the week-56 visit). Among all randomized patients, 273 patients (35%) withdrew before the end of the study (placebo group, 44%; adalimumab 40 mg every other week, 36%; adalimumab 40 mg weekly, 25%).

Of the 854 patients enrolled in the trial, 499 (58%) responded to adalimumab induction and were randomized. These 499 patients comprised the randomized responder population assessed in the predefined primary efficacy end point analysis. The 279 nonresponders who were randomized at week 4 were included in the safety analysis. Baseline characteristics of the week-4 responders compared with nonresponders were similar (Table 1).

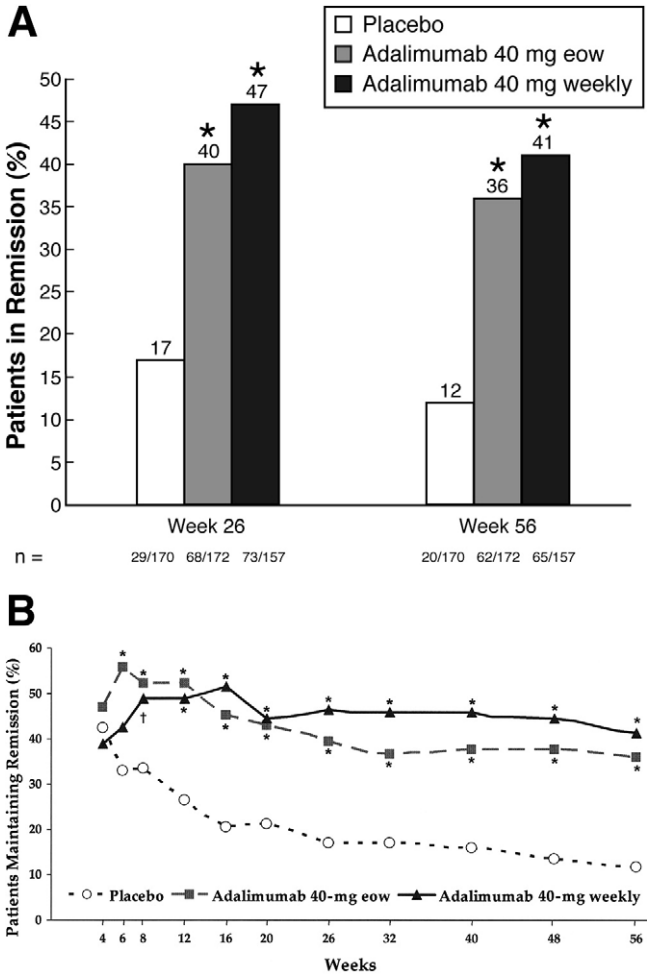

Figure 2. (*A*) Clinical remission at weeks 26 and 56 in randomized responder population (week-4 responders). Remission defined as a decrease in CDAI score to <150. *$P < .001$ for pairwise comparison between each adalimumab treatment group and placebo. eow, every other week. (*B*) Clinical remission over time in randomized responder population (week-4 responders). $P < .001$ for adalimumab vs placebo at every time point at/after 6 weeks for 40 mg eow and at/after 12 weeks for 40 mg weekly. *$P = .001$ vs placebo; †$P = .005$ vs placebo.

Among the randomized responder population, 143 patients (29%) withdrew before the end of the study, with the percentage of withdrawals being similar in the placebo (35%) and adalimumab 40-mg every other week groups (33%) and lower in the adalimumab 40-mg weekly group (17%). The most common reason for study discontinuation in all 3 randomized responder groups was adverse events.

Efficacy

The percentage of week-4 randomized responders in remission (CDAI score <150) at weeks 26 and 56 (the primary end point) was significantly greater in both adalimumab treatment groups versus placebo (adalimumab 40-mg every other week 40%, adalimumab 40 mg weekly 47%, and placebo 17% at week 26; adalimumab 40 mg every other week 36%, adalimumab 40 mg weekly

Table 2. Patients With a Decrease From Baseline in CDAI Score ≥100 and ≥70

Clinical response	Treatment group[a]		
	Placebo (n = 170)	Adalimumab every other week (n = 172)	Adalimumab weekly (n = 157)
Decrease from baseline ≥100			
Week 26	45 (26.5)	89 (51.7)	82 (52.2)
Week 56	28 (16.5)	71 (41.3)	75 (47.8)
Decrease from baseline ≥70			
Week 26	48 (28.2)	93 (54.1)	88 (56.1)
Week 56	30 (17.6)	74 (43.0)	77 (49.0)

NOTE. All values are expressed as n (%). $P < .001$ for pairwise comparisons of each active treatment group vs placebo at all end points.
[a]Randomized responders.

41%, and placebo 12% at week 56; $P < .001$ for pairwise comparison between each adalimumab treatment group and placebo) (Figure 2*A*). The differences between the adalimumab 40-mg every other week and adalimumab 40-mg weekly groups at both of these time points were not statistically significant ($P = .22$ at week 26 and $P = .34$ at week 56). The difference in remission rates between adalimumab and placebo treatment groups was seen as early as week 6 and was sustained through week 56 (Figure 2*B*). Of patients in remission at 26 weeks, 81% of each of the adalimumab groups and 48% of the placebo group remained in remission at week 56. The median time in clinical remission for randomized responders achieving remission was 127 days for the placebo group and 378 days for the adalimumab 40-mg every other week group ($P = .002$). This variable was greater than 392 days for the adalimumab 40-mg weekly group ($P < .001$).

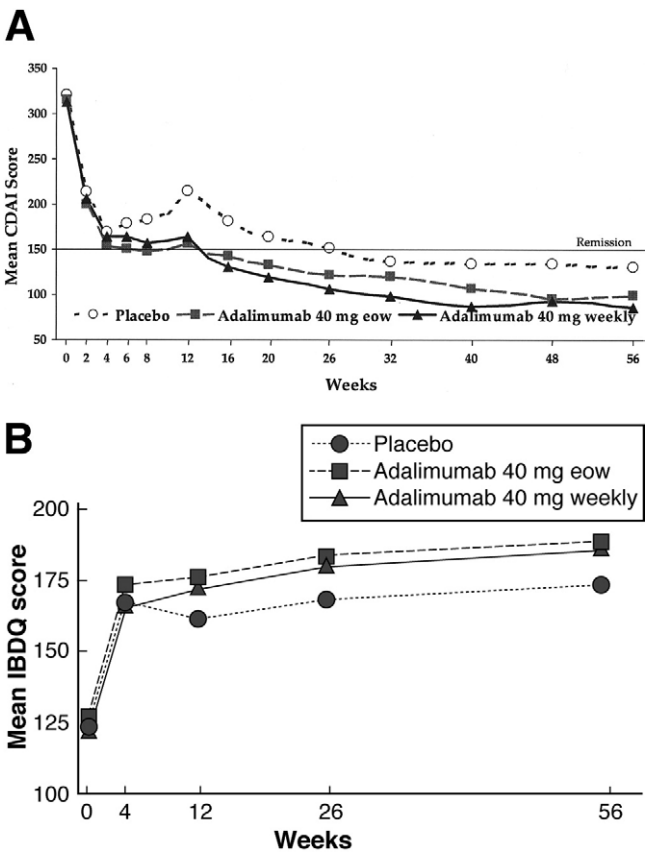

Figure 3. Mean (*A*) CDAI and (*B*) IBDQ total scores over time among week-4 responders. eow, every other week.

Adalimumab also maintained significantly greater rates of response (CDAI score decrease from baseline of ≥70 and ≥100) for randomized responders compared with placebo at both weeks 26 and 56 (Table 2; $P < .001$ for pairwise comparisons of each active treatment group vs placebo at both end points). Mean CDAI decreased to a significantly greater extent over time in the adalimumab groups versus the placebo group (Figure 3*A*). Similarly, mean IBDQ scores improved to a greater extent over time among adalimumab-treated patients (Figure 3*B*).

Subgroup efficacy. Results of clinical remission by subgroups are described in Table 3. Greater percentages of adalimumab-treated patients than placebo-treated patients achieved remission at both week 26 and week 56, regardless of baseline CRP concentration.

At enrollment, 47% of patients were receiving the immunosuppressants azathioprine, 6-mercaptopurine, or methotrexate, and 50% had received a TNF antagonist before baseline. Adalimumab was significantly superior to placebo for long-term treatment of CD irrespective of concomitant immunosuppressive therapies.

Patients naive to TNF-antagonist therapy and patients experienced with TNF-antagonist therapy both achieved statistically significantly greater remission rates compared with placebo. However, the percentage of patients who were in clinical remission at week 26 was numerically greater for the subgroup of patients naive to TNF-antagonist therapy versus those with a history of TNF-antagonist therapy. Similar findings were observed at week 56.

Corticosteroid discontinuation response. Of the randomized responders at week 26, 3%, 35%, and 30% of patients treated with placebo, adalimumab 40 mg every other week, and adalimumab 40 mg weekly, respectively, achieved corticosteroid-free remission ($P < .001$ for each adalimumab group vs placebo). At week 56, 6%, 29%, and 23% of patients treated with placebo, adalimumab 40 mg

Table 3. Remission Rates Stratified by Baseline CRP Concentration, Immunosuppressive Therapy Use, and Previous TNF-Antagonist Experience

Subgroup	Placebo	Adalimumab 40 mg every other week[a]	Adalimumab 40 mg weekly
Week 26			
CRP <1 mg/dL	15/85 (18)	37/95 (39)	31/82 (38)
CRP ≥1 mg/dL	14/85 (17)	31/76 (41)	42/75 (56)
With immunosuppressant	21/131 (16)	53/136 (39)	53/121 (44)
Without immunosuppressant	8/39 (21)	15/36 (42)	20/36 (56)
TNF-antagonist experienced	13/81 (16)	27/85 (32)	30/71 (42)
TNF-antagonist naive	16/89 (18)	41/87 (47)	43/86 (50)
Week 56			
CRP <1 mg/dL	11/85 (13)	34/95 (36)	27/82 (33)
CRP ≥1 mg/dL	9/85 (11)	28/76 (37)	38/75 (51)
With immunosuppressant	15/131 (12)	50/136 (37)	47/121 (39)
Without immunosuppressant	5/39 (13)	12/36 (33)	18/36 (50)
TNF-antagonist experienced	8/81 (10)	26/85 (31)	24/71 (34)
TNF-antagonist naive	12/89 (14)	36/87 (42)	41/86 (48)

NOTE. All values are expressed as n (%).
[a]CRP concentration was not available for 1 patient.

every other week, and adalimumab 40 mg weekly, respectively, achieved corticosteroid-free remission ($P < .001$ for adalimumab 40 mg every other week vs placebo; $P = .008$ for adalimumab 40 mg weekly vs placebo) (Figure 4).

The percentage of randomized responders who discontinued corticosteroid use and remained corticosteroid-free for at least 90 days plus achieved clinical remission at weeks 26 and 56 (sustained corticosteroid-free remission) also was greater in the adalimumab treatment groups versus placebo. At week 26, 3%, 19%, and 15% of patients treated with placebo, adalimumab 40 mg every other week, and adalimumab 40 mg weekly, respectively, achieved sustained corticosteroid-free remission ($P = .006$ for adalimumab 40 mg every other week vs placebo; $P = .019$ for adalimumab 40 mg weekly vs placebo). At week 56, 5%, 29%, and 20% of patients treated with placebo, adalimumab 40 mg every other week, and adalimumab 40 mg weekly, respectively, achieved sustained corticosteroid-free remission ($P < .001$ for adalimumab 40 mg every other week vs placebo; $P = .006$ for adalimumab 40 mg weekly vs placebo).

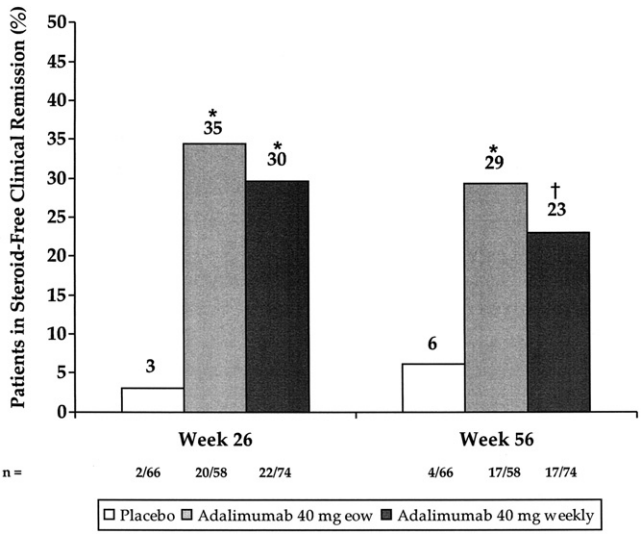

Figure 4. Percentage of patients receiving corticosteroids at baseline who discontinued corticosteroid use and achieved clinical remission (randomized responder population) at weeks 26 and 56. Remission was defined as a decrease in CDAI score to <150. *$P < .001$; †$P = .008$.

Fistula response. Complete fistula closure (closure of all fistulas that were draining at screening and baseline visits) was achieved in a greater percentage of adalimumab-treated patients versus those receiving placebo in the randomized population at both week 26 and week 56 (30% and 13% for combined adalimumab groups and placebo group, respectively, at week 26 [$P = .043$] and 33% and 13% for combined adalimumab groups and placebo group, respectively, at week 56 [$P = .016$]) (Figure 5*A*). Of patients with complete fistula closure at week 26, 100% continued to have complete fistula closure at week 56 (Figure 5*B*).

Safety

During the open-label induction period, 59.4% of patients (507/854) experienced adverse events and 6.3% of patients (54/854) discontinued treatment because of an adverse event (Table 4). The most common adverse events during open-label induction were headache (51/854 [5.9%]) and nausea (45/854 [5.3%]). Serious adverse events were infrequent during open-label induction (45/854 [5.3%]) and included one case of multiple sclerosis. Infectious adverse events occurred in 130 patients (15.2%), and serious infectious adverse events occurred in 10 patients (1.2%) during this period. One death occurred during the open-label induction (discussed in the following text).

During double-blind treatment, adverse events occurred at similar frequencies in the adalimumab and

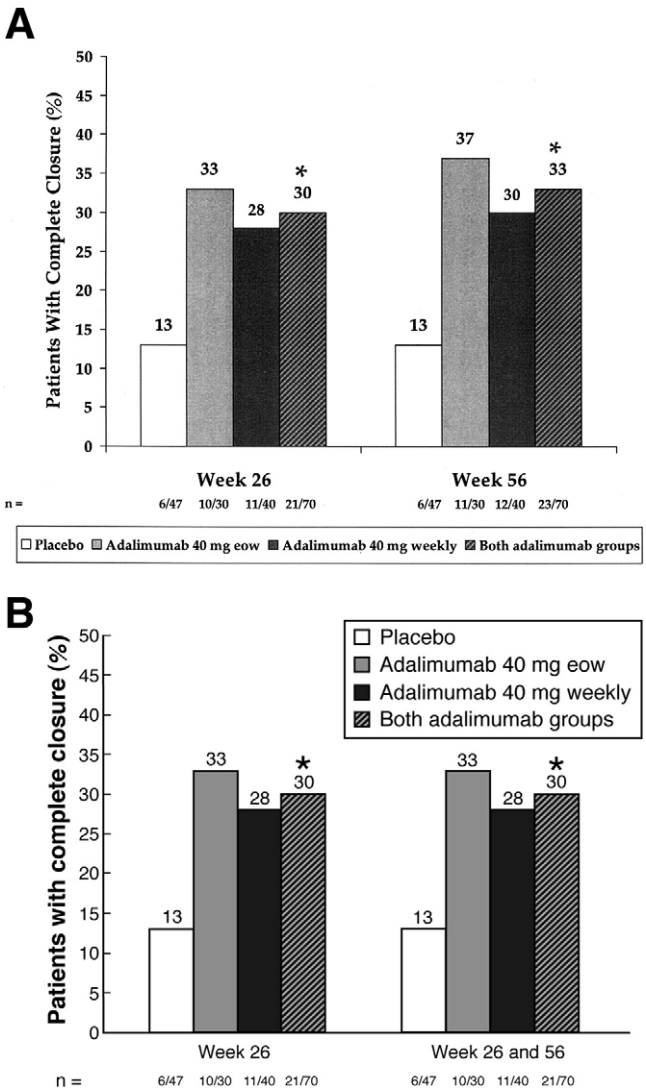

Figure 5. (*A*) Closure of draining fistulas (defined as closure of all fistulas draining at baseline for at least 2 consecutive visits) at weeks 26 and 56 during double-blind therapy in the randomized population of patients with draining fistulas at screening and baseline visits. Note that statistical analyses were not performed on individual adalimumab groups. *P = .043 for combined adalimumab groups versus placebo at week 26; P = .016 for combined adalimumab groups versus placebo at week 56. n, number of patients with fistulas at baseline; eow, every other week. (*B*) Patients with maintenance of healing of draining fistulas at weeks 26 and 56. *P = .043 for combined adalimumab groups versus placebo.

placebo groups (Table 4). A greater percentage of patients in the placebo group discontinued treatment because of an adverse event (13.4%) than in the adalimumab groups (6.9% and 4.7% for 40 mg every other week and 40 mg weekly groups, respectively). Exacerbation of CD, as judged by the investigator, was the most commonly reported adverse event that led to premature discontinuation from the study during the double-blind period (7.7% placebo, 1.9% adalimumab 40 mg every other week, and 1.2% adalimumab 40 mg weekly). Again, reporting exacerbation of CD as an adverse event was independent of meeting the protocol criteria for disease flare, remission failure, or other protocol-driven requirement for switching to open-label therapy.

During the double-blind period, exacerbation of CD was reported significantly more frequently among placebo-treated patients (32.2%) than adalimumab-treated patients (19.6% and 18.7% for 40-mg every other week and 40-mg weekly groups, respectively; $P < .001$ vs placebo). Other adverse events that were reported by at least 5% of patients in one of the 3 treatment groups, and at significantly different rates among treatment groups, were headache, fatigue, and urinary tract infections (Table 4). Injection-site reactions also occurred more frequently in both adalimumab groups than in the placebo group. Injection-site reactions were generally mild to moderate. The remaining adverse events that were reported in at least 5% of patients in one of the 3 treatment groups occurred in all groups at similar rates and included arthralgia, nasopharyngitis, nausea, abdominal pain, pyrexia, upper respiratory tract infection, influenza, diarrhea, and pharyngolaryngeal pain.

During the double-blind period, serious adverse events occurred in a greater percentage of placebo-treated patients (15.3%) versus those randomized to adalimumab (9.2% and 8.2% for 40-mg every other week and 40-mg weekly groups, respectively; $P < .05$ vs placebo). Infectious adverse events occurred in 36.8% of patients in the placebo group versus 46.2% of patients in the adalimumab 40-mg every other week group ($P < .05$ vs placebo) and 44.4% of those treated with adalimumab 40 mg weekly ($P = .089$) (Table 4). Serious infectious adverse events were infrequent, occurring in 2.7% of patients in each of the adalimumab groups, compared with 3.4% of patients in the placebo group. The specific types of serious infectious adverse events observed are shown in Table 5. Although the sample sizes were small, the rate of serious infections appeared to be similar regardless of baseline immunosuppressant use (4 events with vs 3 events without immunosuppressants with adalimumab 40 mg every other week; 3 vs 4 events, respectively, with adalimumab 40 mg weekly; 3 vs 6 events, respectively, with placebo).

One patient died after entering the trial as a result of a pulmonary embolism. The patient received the open-label 80-mg/40-mg induction regimen of adalimumab and on day 15 died of a pulmonary embolism. Contributing risk factors included advanced age (72 years) and a history of pulmonary embolism, hypertension, and atrial fibrillation. The event was deemed by the investigator as not related to the study drug.

One female patient randomized to the placebo group was diagnosed with cancer of the right breast 77 days after the start of study drug (26 days posttreatment) during double-blind treatment. The patient received both open-label induction doses of adalimumab and was withdrawn from the study after 3 weeks of double-blind

Table 4. Summary of Safety Analyses for Open-Label Induction and Double-Blind Period

Variable	Induction	Double-blind period		
	Adalimumab 80/40 mg (N = 854)	Placebo (n = 261)	Adalimumab 40 mg every other week (n = 260)	Adalimumab 40 mg weekly (n = 257)
Adverse events	507 (59.4)	221 (84.7)	231 (88.8)	220 (85.6)
Adverse events leading to discontinuation of study drug	54 (6.3)	35 (13.4)	18 (6.9)[a]	12 (4.7)[a]
Select adverse events occurring at a frequency of at least 5% in either the adalimumab or placebo groups[b]				
CD		84 (32.2)	51 (19.6)[c]	48 (18.7)[c]
Arthralgia		23 (8.8)	27 (10.4)	34 (13.2)
Nasopharyngitis		18 (6.9)	29 (11.2)	31 (12.1)
Headache	51 (6.0)	15 (5.7)	25 (9.6)	30 (11.7)[a]
Nausea	45 (5.3)	16 (6.1)	19 (7.3)	22 (8.6)
Fatigue		6 (2.3)	11 (4.2)	20 (7.8)[d]
Abdominal pain		17 (6.5)	20 (7.7)	19 (7.4)
Pyrexia		14 (5.4)	14 (5.4)	17 (6.6)
Upper respiratory tract infection		16 (6.1)	12 (4.6)	16 (6.2)
Injection site reaction		1 (0.4)	11 (4.2)[d]	15 (5.8)[c]
Urinary tract infection		4 (1.5)	11 (4.2)	15 (5.8)[d]
Influenza		13 (5.0)	14 (5.4)	13 (5.1)
Diarrhea		15 (5.7)	10 (3.8)	12 (4.7)
Pharyngolaryngeal pain		14 (5.4)	11 (4.2)	7 (2.7)
Serious adverse events	45 (5.3)	40 (15.3)	24 (9.2)[a]	21 (8.2)[a]
Infectious adverse events	130 (15.2)	96 (36.8)	120 (46.2)[a]	114 (44.4)
Serious infectious adverse events	10 (1.2)	9 (3.4)	7 (2.7)	7 (2.7)
Selected injection site reactions				
Bruising	1 (0.1)	2 (0.8)	6 (2.3)	2 (0.8)
Erythema	7 (0.8)	0	7 (2.7)[a]	3 (1.2)
Hemorrhage	4 (0.5)	2 (0.8)	5 (1.9)	0
Irritation	39 (4.6)	2 (0.8)	10 (3.8)[a]	7 (2.7)
Pain	41 (4.8)	2 (0.8)	5 (1.9)	4 (1.6)
Pruritus	2 (0.2)	0	3 (1.2)	2 (0.8)
Reaction	17 (2.0)	1 (0.4)	11 (4.2)[d]	15 (5.8)[c]

NOTE. All values are expressed as n (%).
[a]$P < .05$ vs placebo.
[b]Including injection site reactions as noted.
[c]$P < .001$ vs placebo.
[d]$P < .01$.

treatment with placebo. She underwent wide excision and axillary node resection. Pathology results revealed infiltrating ductal adenocarcinoma. The event was considered serious and probably not related to study drug by investigators.

Two cases of pulmonary tuberculosis were reported during the study in patients who, at baseline, were purified protein derivative-negative and had normal findings on chest radiographs. One patient had received open-label adalimumab 40 mg every other week for 197 days after 56 days of double-blind treatment with adalimumab 40 mg every other week, and the other had received open-label adalimumab for a total of 260 days (31 days at 40 mg every other week and 229 days at 40 mg weekly) after 77 days of double-blind treatment with adalimumab 40 mg weekly. This latter patient also had received both prednisone and azathioprine as concomitant medications.

Adalimumab concentration, antibodies to adalimumab, antinuclear antibodies, and anti–double-stranded DNA antibodies were not measured in this study.

Discussion

Adalimumab, a fully human immunoglobulin G1 monoclonal antibody, is effective in inducing and maintaining long-term (56-week) clinical remission in patients with moderate to severe CD who have responded to induction therapy with adalimumab. Significant treatment differences between adalimumab and placebo groups in terms of remission and CDAI 100-point and 70-point responses were noted early (within 4 weeks after randomization) and were maintained throughout the double-blind phase. Consistent with these results, mean changes in CDAI scores and mean IBDQ total scores

Table 5. Select Serious Adverse Events of Clinical Interest for Open-Label Induction and Double-Blind Period

	Induction	Double-Blind period		
	Adalimumab 80/40 mg (N = 854)	Placebo (n = 261)	Adalimumab 40 mg every other week (n = 260)	Adalimumab 40 mg weekly (n = 257)
Infections and infestations	10 (1.2)	9 (3.4)	7 (2.7)	7 (2.7)
Abscess	7 (0.8)	5 (1.9)	3 (1.2)	5 (1.9)
Tuberculosis	0 (0.0)	0 (0.0)	0 (0.0)[a]	0 (0.0)[a]
Other opportunistic infections	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Wound infection, sepsis, postoperative infection	3 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Cancer	0 (0.0)	1 (0.4)[b]	0 (0.0)	0 (0.0)
Multiple sclerosis	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Serum sickness	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Death	1 (0.1)[c]	0 (0.0)	0 (0.0)	0 (0.0)

NOTE. All values are expressed as n (%).
[a]One case of tuberculosis occurred in each adalimumab treatment group during postrandomization open-label therapy.
[b]Breast cancer.
[c]Pulmonary embolism.

reflected significantly lower disease activity and improved quality of life in patients receiving adalimumab versus those receiving placebo. In addition, a significantly greater percentage of patients receiving adalimumab maintenance treatment were able to discontinue corticosteroids and achieve corticosteroid-free remission at 26 and 56 weeks compared with patients receiving placebo. Among patients with fistulas at baseline, complete fistula closure occurred in a greater percentage of patients receiving adalimumab maintenance therapy compared with those receiving placebo. This response was maintained because all patients who achieved fistula closure at week 26 with adalimumab maintained closure through week 56.

The results presented here of effective maintenance therapy with subcutaneously administered adalimumab in patients with CD support and extend the findings of the CLASSIC-I and -II trials of adalimumab for induction and maintenance of remission in CD.[25–27] In the CLASSIC-I induction trial, 3 adalimumab induction-loading doses were evaluated: 40 mg/20 mg, 80 mg/40 mg, and 160 mg/80 mg. These induction-loading dose regimens were designed to achieve adalimumab concentrations at week 4 that would equate to steady-state blood concentrations achieved with maintenance dosing with adalimumab 20 mg every other week, 40 mg every other week, and 40 mg weekly. The only induction-loading dose regimen that achieved statistical significance for remission rates versus placebo was 160 mg, followed in 2 weeks by 80 mg. Because CHARM began before the availability of these data, an induction-loading dose regimen of 80 mg followed in 2 weeks by 40 mg was chosen (which equated to 40 mg every other week maintenance dosing). Although uncontrolled remission rates at the end of the open-label induction phase were not a primary end point in CHARM, which was designed and powered to evaluate the efficacy of adalimumab for maintenance therapy, the induction-loading dose regimen used (80 mg/40 mg) provided similar response rates (70-point decrease in CDAI of 58%) to both the 80 mg/40 mg and 160 mg/80 mg regimens in CLASSIC I (59% for each regimen).[25] In the randomized arm of the CLASSIC-II maintenance trial, 74%–93% of patients in clinical remission at the end of CLASSIC I, and who remained in remission after 2 open-label doses of adalimumab in CLASSIC II and continued to receive active maintenance therapy (either adalimumab 40 mg every other week or weekly), were in remission at 24 and 56 weeks of CLASSIC II.[26] The results of the current trial (CHARM), which had a larger sample size than CLASSIC II (854 vs 299), confirm that adalimumab is more effective than placebo for long-term (56-week) maintenance of remission. In this study, efficacy outcomes with adalimumab every other week dosing were not statistically significantly different from weekly dosing. CLASSIC I supports the use of an induction dose of adalimumab of 160 mg/80 mg to achieve remission, although lower dosages resulted in significant improvement as measured by the less stringent measure of a 70-point response in CDAI. Data from both CLASSIC II and CHARM support the use of a maintenance dosing regimen of adalimumab 40 mg every other week for patients with moderately to severely active CD.

Efficacy results from this study (CHARM) of adalimumab are similar to the response and remission rates reported with the intravenously administered chimeric immunoglobulin G1 monoclonal antibody infliximab. In addition, adalimumab demonstrated statistically significant and clinically meaningful effects on fistula closure, such as has been previously demonstrated for inflix-

imab.[4,6] Also comparable to previous reports with infliximab, clinical remission with adalimumab was maintained after the discontinuation of corticosteroids.[3] Reported uniquely in CHARM, however, is the ability to sustain corticosteroid-free remission for at least 90 days.

In addition, adalimumab has been evaluated in patients who are intolerant of or who have failed to respond to infliximab in a number of small studies.[28–33] Collectively, these studies suggest that patients with CD who have lost their responses to or are intolerant of infliximab may benefit from switching to adalimumab. Results from CHARM demonstrate that patients naive to TNF antagonists achieved slightly better results than those who had received TNF antagonists in the past; however, differences between these subgroups were not statistically significant, and both treatment subgroups achieved greater efficacy than placebo. A large, randomized controlled trial of adalimumab in patients selected for intolerance and/or loss of efficacy due to infliximab failure (the GAIN trial) has been completed, and the results were presented in late 2006.[34]

Induction and maintenance therapy with adalimumab was generally well-tolerated in this study. Rates of discontinuation due to adverse events were low and were greater in placebo-treated patients versus those receiving adalimumab during double-blind treatment. The overall incidence of adverse events was similar between the placebo and adalimumab groups. Similarly, rates of serious adverse events were low overall but occurred more frequently in placebo-treated patients. These differences were primarily because a greater percentage of patients receiving placebo experienced serious and nonserious events related to active CD. Overall, the safety profile exhibited by adalimumab in this trial is consistent with previous experience with adalimumab from more than 150,000 patients for the treatment of CD, rheumatoid arthritis, ankylosing spondylitis, psoriasis, and psoriatic arthritis.[16,25,26,35,36] One death due to pulmonary embolism in a patient with a history of pulmonary embolism occurred during open-label induction and was deemed unrelated to study drug. One malignancy (a breast cancer) occurred in a patient receiving placebo during the double-blind phase and was deemed probably not related to study drug. No cases of lymphoproliferative disorder were reported. The 2 cases of tuberculosis reported were deemed possibly and probably related to study drug, respectively. Tuberculosis has been reported with all TNF antagonists. The 2 cases reported in this study occurred despite screening, suggesting that this method of screening has limitations. There was one reported event of multiple sclerosis early in open-label induction. Reports of multiple sclerosis have been linked to the use of all TNF antagonists. There were no reports of demyelinating disease, lupus, congestive heart failure, or coagulation disorder. Although injection-site reactions occurred more frequently with adalimumab, only 4%–6% of patients developed these reactions and they were generally mild or moderate and did not lead to discontinuation of adalimumab therapy.

Although immunogenicity was not evaluated in CHARM, the occurrence of anti-adalimumab antibodies was evaluated among patients with CD in the CLASSIC-II maintenance study. During the 52-week study, 2 of 54 patients (3.7%; one in the placebo group and one in the adalimumab every other week group) in the randomized arm and 6 of 215 patients (2.8%) in the open-label arm of the study were positive for anti-adalimumab antibodies.[26,27]

The results of this study show that adalimumab 40 mg every other week and 40 mg weekly are more effective than placebo in maintaining clinical remission and response in patients with moderate to severe CD through 56 weeks. Adalimumab is also effective for maintaining corticosteroid-free remission and completely closing fistulas. No differences in efficacy between the 40-mg every other week and 40-mg weekly dosing regimens of adalimumab were observed. Adalimumab was generally well-tolerated, with a safety profile consistent with previous experience with this drug. Our findings show that adalimumab represents an effective and well-tolerated, patient self-administered therapeutic option to induce and maintain remission in patients with moderate to severe CD.

Appendix 1. CHARM Study Investigators and Sites

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A list of the CHARM study investigators and sites appears in Appendix 1.

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