



Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease

Mamoru Watanabe ^{a,*}, Toshifumi Hibi ^b, Kathleen G. Lomax ^c,
Susan K. Paulson ^c, Jingdong Chao ^c, M. Shamsul Alam ^d, Anne Camez ^e
On behalf of the study investigators ¹

^a Tokyo Medical & Dental University, Tokyo, Japan

^b Keio University School of Medicine, Tokyo, Japan

^c Abbott, Abbott Park, IL, United States

^d Abbott Park, IL, United States

^e Abbott GmbH & Co. KG, Ludwigshafen, Germany

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Abstract

Background and aims: Adalimumab has been shown to be efficacious and well-tolerated in Western patients with Crohn's disease. These 2 randomized, double-blind clinical trials evaluated adalimumab efficacy and safety in Japanese patients with moderate to severe Crohn's disease. **Methods:** 90 patients enrolled in the induction trial and were randomized to receive adalimumab 160/80 mg, adalimumab 80/40 mg or placebo at Weeks 0/2. At Week 4, patients who achieved a decrease in CDAI ≥ 70 points versus Baseline entered the maintenance trial and were randomized to adalimumab 40 mg every other week or placebo for 52 weeks. All other patients received 4 more weeks of blinded adalimumab before entering the open-label portion of

Abbreviations: CD, Crohn's disease; PPD, purified protein derivative; TPN, total parenteral nutrition; CDAI, CD activity index; CR-70, decrease in CDAI score from Baseline ≥ 70 ; CR-100, decrease in CDAI score from Baseline ≥ 100 ; eow, every other week; 6-MP, 6-mercaptopurine; BCG, Bacillus Calmette-Guérin; IOIBD, International Organization of Inflammatory Bowel Disease; PCS, physical component summary; MCS, mental component summary; SF-36, Short Form-36 Health Survey; IBDQ, Inflammatory Bowel Disease Questionnaire; AAA, anti-adalimumab antibody; AAA+, patients positive for anti-adalimumab antibody; FAS, full analysis set; mFAS, modified full analysis set; HRQOL, health-related quality of life; IMM, immunomodulator; 5-ASA, 5-aminosalicylate.

* Corresponding author at: Department of Gastroenterology, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8510, Japan. Tel.: +81 3 3813 6111; fax: +81 3 5803 0262.

E-mail address: mamoru.gast@tmd.ac.jp (M. Watanabe).

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the maintenance trial. At/after Week 4 of the maintenance trial, blinded patients who flared/failed to respond entered the open-label portion. Open-label maintenance patients received adalimumab 40 mg every other week with the option of 80 mg every other week for flare/non-response.

Results: Clinical remission rates at Week 4 in the induction trial were 33.3%, 17.6% and 13.0% in the adalimumab 160/80 mg, adalimumab 80/40 mg and placebo groups, respectively. Maintenance remission rates were 38.1% for adalimumab and 9.1% for placebo at Week 52. Anti-TNF naïve patients achieved greater efficacy than anti-TNF exposed patients. Patients randomized to adalimumab achieved greater quality of life improvement versus placebo. There were no clinically relevant differences in safety between adalimumab and placebo.

Conclusions: Adalimumab is effective and well-tolerated for inducing and maintaining clinical remission in Japanese patients with moderate to severe Crohn's disease. NCT00445939; NCT00445432.

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1. Introduction

The incidence and prevalence of Crohn's disease (CD) in Japan are lower than in other regions, although these have been shown to be increasing in Japan,¹ as they are in Western countries. Characteristics of CD in Japanese patients are the same as in Western patients. Though the positioning of nutritional therapy differs, the same drugs are used in Japanese and Western patients, and data supporting the use of anti-tumor necrosis factor (TNF) agents in the treatment of Japanese patients with CD are available.²

Adalimumab (HUMIRA, Abbott Laboratories, Abbott Park, Illinois, USA), a fully human monoclonal antibody that targets TNF, is approved for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, CD, psoriasis, and juvenile idiopathic arthritis in the United States, Europe, and elsewhere.³ In Japan, adalimumab is approved for the treatment of rheumatoid arthritis, psoriatic arthritis, psoriasis, and ankylosing spondylitis. Adalimumab was also approved for the treatment of CD in Japan on the basis of the present trials. Adalimumab has been shown to be effective for the induction and maintenance of remission in Western patients with moderate to severe CD.⁴ Adalimumab is also effective in patients who have had an inadequate response to conventional therapy or who have lost response to or are unable to tolerate infliximab, the chimeric monoclonal antibody to TNF.⁵ In addition, adalimumab has been shown to provide rapid and sustained improvements in quality of life, both physical and psychological, in adults with active CD in Western countries.^{6–9}

The objectives of these 2 multicenter clinical trials were to determine the efficacy and safety of adalimumab in inducing and maintaining remission, and to determine the effect of adalimumab on quality of life in Japanese patients with moderate to severe CD. In addition, the pharmacokinetics and immunogenicity of adalimumab treatment in Japanese patients were assessed.

2. Methods

2.1. Patients

This report describes results from 2 related clinical trials conducted in Japanese patients: first, a multicenter, randomized, double-blind, placebo-controlled trial

(NCT00445939, January 2007 to December 2007) for induction of remission of CD; then a follow-on multicenter, placebo-controlled 52-week trial (NCT00445432, March 2007 to December 2008) for maintenance of remission.

Japanese adults and adolescents ≥ 15 and ≤ 75 years of age, with a diagnosis of moderate to severely active CD (CD Activity Index [CDAI] score of 220–450) for >4 months and a diagnosis of ileal, colonic or ileocolonic CD confirmed by endoscopy or radiologic evaluation, were included. Previous exposure to anti-TNF agents other than adalimumab was allowed; primary non-responders to prior anti-TNF therapy were excluded. Women of childbearing potential were not pregnant or breast-feeding and were practicing an acceptable method of birth control throughout the trial and for 150 days after the last study drug administration. Patients provided written informed consent and complied with the requirements of this study protocol. Written informed consent was provided by a parent or legal guardian if the patient was <20 years old.

Patients were excluded for a diagnosis of ulcerative colitis or indeterminate colitis; history of cancer, lymphoma, leukemia or lymphoproliferative disease; active tuberculosis, chest X-ray findings suggestive of previous or current tuberculosis infection, "strongly positive" purified protein derivative (PPD) skin test with induration and erythema ≥ 10 mm with either bulla, necrosis or double redness (concentric surrounding of strong redness by weaker redness)¹⁰; human immunodeficiency virus infection; persistent chronic infections or recent infections unrelated to CD, requiring hospitalization or treatment with anti-infectives (intravenous within 28 days or oral within 14 days); history of neurologic symptoms suggestive of central nervous system demyelinating disease; presence or suspicion of abscess; surgical bowel resections within the past 6 months; positive *C. difficile* stool assay at Screening; body weight <30 kg; clinically significant abnormalities found during the electrocardiogram evaluation or laboratory assessment at the Screening visit; or a poorly controlled medical condition or any condition which, in the opinion of the investigator, would put the patient at risk by participation in the trial. Patients who received total parenteral nutrition within 14 days before Baseline or enteral nutrition >1200 kcal/day were excluded, as were patients who used infliximab or any biological agent within 8 weeks of Baseline. Previous treatment with adalimumab or participation in an

adalimumab clinical trial, any prior exposure to natalizumab, and receipt of any investigational chemical agent in the past 28 days or 5 half-lives prior to Baseline were not allowed.

2.2. Study design

In the induction trial, patients were randomly assigned (3:3:2) to receive induction therapy with adalimumab 160/80 mg, adalimumab 80/40 mg, or placebo at Baseline and Week 2 (Fig. 1). Patients achieving a clinical response 70 (CR-70, decrease from Baseline in CDAI ≥ 70 points) at Week 4 in the induction trial entered the blinded portion of the 52-week maintenance trial and were randomly assigned (1:1) to receive adalimumab 40 mg every other week (eow) or placebo. CR-70 non-responder patients at Week 4 in the induction trial continued for a further 4 weeks in the induction trial and were given double-blind adalimumab, with the dose of adalimumab depending on the induction regimen to which the patients were initially randomized. Week 4 CR-70 non-responder patients who had been randomized to placebo in the induction trial were given blinded adalimumab 160/80 mg induction therapy at Weeks 4 and 6 in the induction trial, and then entered the open-label portion of the maintenance trial. Week 4 CR-70 non-responder patients who had been randomized to adalimumab at either induction dose in the induction trial were given blinded adalimumab 40 mg at Weeks 4 and 6, and then entered the open-label portion of the maintenance trial. To accommodate the differing lengths of the induction trial for the CR-70 responders (4 weeks) and the CR-70 non-responders (8 weeks), the Baseline week of the maintenance trial is called Week 0x and the numbering of the following weeks includes "x" to describe the follow-on nature of the maintenance trial.

At or after Week 4x, patients in the blinded portion of the maintenance trial who flared could enter the open-label portion. Patients in the open-label portion received adalimumab 40 mg eow with the ability to increase the adalimumab dose to 80 mg eow in case of flare or non-response; the escalation dose of 80 mg eow has been approved in Japan, instead of 40 mg weekly, for other indications including rheumatoid arthritis, psoriasis, and ankylosing spondylitis. Flare was defined as a recurrence of very active disease, specifically an increase of ≥ 70 points in CDAI when compared with Week 0x in the maintenance trial and a CDAI > 220 . Lack of response was defined as not attaining a CDAI decrease of ≥ 70 points compared with Week 0 of the induction trial for 2 consecutive visits, at least 2 weeks apart.

Concomitant use of immunomodulators (azathioprine and 6-mercaptopurine), aminosaliclates, and Crohn's-related antibiotics, was permitted in the induction and maintenance trials, provided that the doses remained stable. Stable doses of corticosteroids (≤ 40 mg/day of prednisolone or equivalent), and stable enteral nutrition ≤ 1200 kcal/day were permitted. No changes of Crohn's-related concomitant therapies were allowed during the induction trial. At Week 4x of the maintenance trial, patients who had experienced a significant improvement in their Crohn's symptoms (defined as a CDAI decrease of ≥ 70 points compared to Baseline of induction trial) could taper enteral nutritional therapy and

corticosteroid doses, with the possibility to increase back to the amount at Week 0x if the disease was aggravated. In the open-label treatment group in the maintenance trial, patients were allowed to reduce or discontinue Crohn's-related concomitant treatments after 12 weeks of exposure to open-label adalimumab, with the possibility to increase back to the initial dose if the patient experienced a loss of clinical response. In both the induction and maintenance trials, patients could receive isoniazide for the prophylaxis of tuberculosis infection in patients with induration ≥ 5 mm on the PPD skin test, irrespective of the Bacillus Calmette-Guérin (BCG) vaccination status.

2.3. Endpoints

2.3.1. Induction trial

The CDAI score and International Organization of Inflammatory Bowel Disease¹¹ (IOIBD) score were assessed at Baseline and every 2 weeks. The mental component summary (MCS) and physical component summary (PCS) of the Short Form-36 (SF-36) Health Survey and the Inflammatory Bowel Disease Questionnaire (IBDQ) were assessed at Baseline and every 4 weeks.^{12–14} The primary endpoint was the proportion of patients in clinical remission (CDAI < 150) at Week 4. Secondary endpoints included the proportion of patients in clinical remission at Week 2 and with clinical response CR-100 or clinical response CR-70 (CDAI decrease of ≥ 100 or ≥ 70 from Baseline, respectively) at Week 2 and Week 4. Additional secondary endpoints included changes from Baseline in CDAI and IOIBD at Week 2 and Week 4 and changes from Baseline in SF-36 MCS and PCS, and IBDQ scores in each treatment group at Week 4. In *post-hoc* analyses, clinical remission, CR-100, and CR-70 at Week 4 were assessed in each treatment group after stratification by patients' previous use of anti-TNF therapies.

2.3.2. Maintenance trial

The CDAI and IOIBD were measured at Baseline (Week 0x) and every 4 weeks to Week 52x in the maintenance trial. The SF-36 MCS and PCS and the IBDQ were assessed at Baseline and Weeks 8x, 24x, and 52x. The primary endpoint was clinical remission (CDAI < 150) at Week 52x in the double-blind portion. Secondary endpoints included the proportion of patients in clinical remission, CR-100, or CR-70 every 4 weeks until Week 52x; changes from Baseline of the induction trial (Week 0) to Week 52x in CDAI, IOIBD, SF-36 MCS and PCS scores and IBDQ in the double-blind portion.

2.3.3. Pharmacokinetics and immunogenicity

Blood samples for serum adalimumab and anti-adalimumab antibody (AAA) assays were collected at Week 1 and prior to dose administration at Weeks 0, 2 and 4 in the induction trial and Weeks 0x, 4x, 8x, 12x, 16x, 20x, 24x, 36x and 52x in the maintenance trial. Adalimumab and AAA samples were analyzed at MDS Pharma Services (Switzerland AG) using validated enzyme-linked immunosorbent assay (ELISA) methods based on a double-antigen technique.¹⁵ The lower limit of quantitation (LLOQ) for adalimumab concentration was established at 3.1 ng/mL in diluted serum or 31.3 ng/mL in undiluted serum. The coefficient of variation (CV) for adalimumab concentration was $\leq 7.0\%$ and the analytical



each collection time. The proportion of patients positive for AAA (AAA+) was calculated and efficacy and safety for AAA+ patients assessed.

2.4.1. Safety

Adverse events (AE), laboratory values, and vital signs were assessed on a routine basis throughout both the induction and maintenance trials. AEs were analyzed using a descriptive analysis. In the induction and maintenance trials, a treatment-emergent AE (TEAE) was defined as any AE with onset from the first dose of study drug, with differing endpoints depending on whether the patient continued in the adalimumab development program or not. Specifically,

for patients who continued in the adalimumab development program, the end-date for reporting TEAEs was at the trial end (Week 4 or 8 for the induction trial; Week 52x for the maintenance trial); for patients who discontinued the trial and did not continue in the adalimumab development program, the end-date for reporting TEAEs was up to 70 days following the last study drug administration. For analysis of the any adalimumab set (combines induction and maintenance trial), a TEAE was defined as any AE with onset from the first dose of adalimumab the patient ever received (which could have been in the induction trial for those randomized to adalimumab, or in the maintenance trial for those randomized to placebo in the induction trial) through

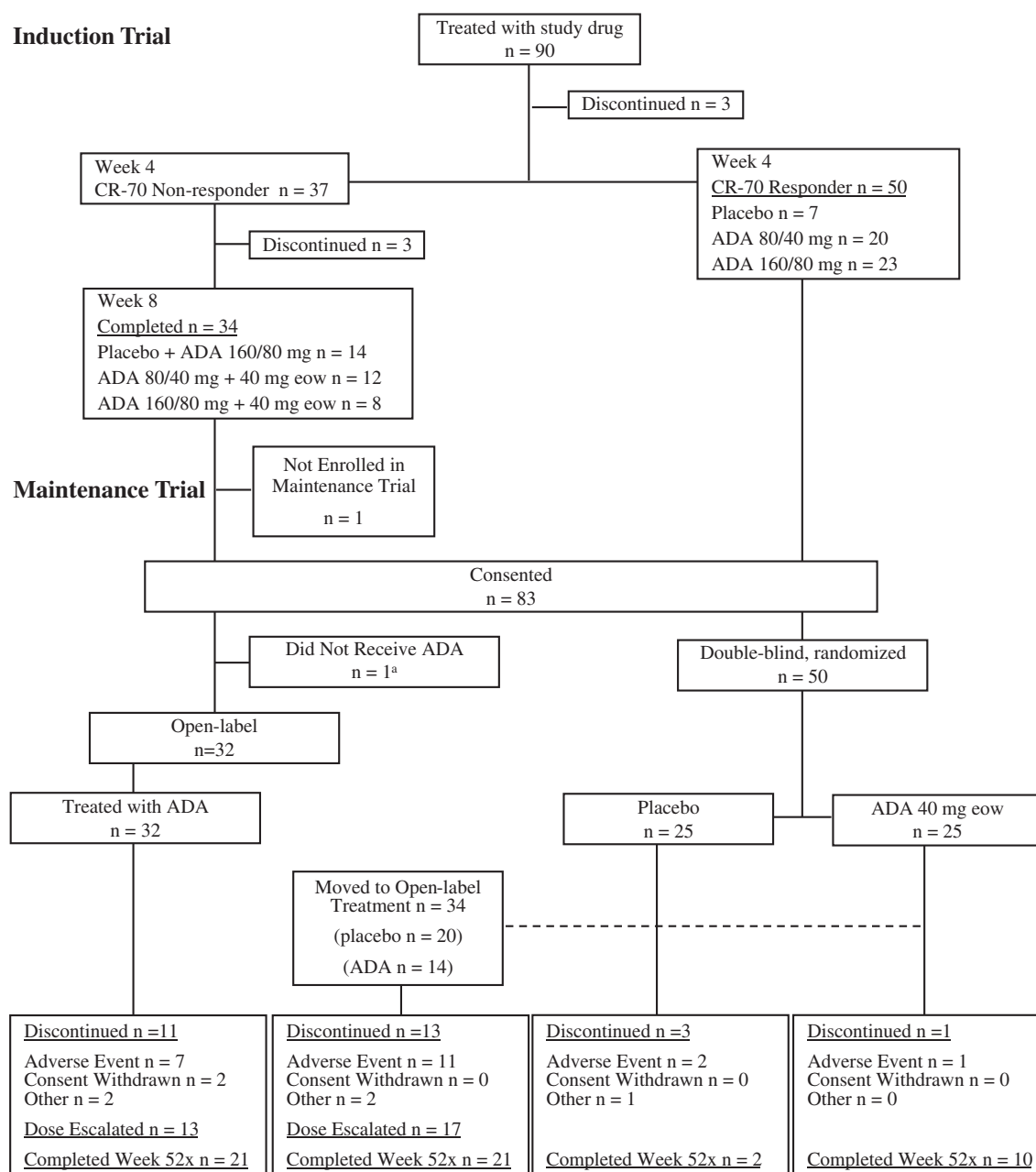


Figure 2 Patient disposition. The "x" designation beside the week numbers indicates the follow-on nature of maintenance trial.

^aOne patient in the adalimumab 160/80 mg + 40 mg eow group in the induction trial enrolled in the maintenance trial but was not dosed. ADA = adalimumab; CR-70 = decrease in CD4I from Baseline ≥ 70 ; eow = every other week.

an end-date up to the last dose received in the maintenance trial if the patient continued after Week 52x, or up to 70 days after the last dose of adalimumab if the patient discontinued either trial. Of note, for any adalimumab set, events that occurred during the placebo period prior to receipt of any adalimumab were excluded.

3. Results

3.1. Patient population

3.1.1. Induction trial

Informed consent was obtained from 108 patients, of which 90 were randomly assigned to receive study drug (adalimumab 160/80 mg, $n=33$; adalimumab 80/40 mg, $n=34$; placebo, $n=23$). 18 patients dropped out of the study prior to randomization. The reasons were ineligibility ($n=13$), serious adverse events ($n=3$), withdrawal of consent ($n=1$) and aggravation of CD ($n=1$).

3.1.2. Maintenance trial

Of 90 patients enrolled in the induction trial, 83 consented to continue in the maintenance trial (for the 7 patients who did not continue, 6 were terminated early from the induction trial due to adverse events and 1 did not continue in the maintenance trial because of the patient's demand); 50 entered the double-blind randomized portion (FAS) and 32 entered the open-label portion (1 patient was not treated). Of the 50 patients who entered the double-blind portion, 43 received adalimumab in the induction trial and were included in the mFAS. Patient disposition for the follow-on maintenance trial is summarized in Fig. 2.

3.2. Baseline characteristics

Baseline demographics, assessments of disease activity, efficacy parameters, health-related quality of life (HRQOL) scales, and concomitant medication use are summarized in Tables 1 and 2. There were no clinically important

Table 1 Baseline characteristics.^a

	Induction trial				Maintenance trial		
	Full analysis set ^b				Full analysis set ^c		
	Placebo $n=23$	Adalimumab 80/40 mg $n=34$	Adalimumab 160/80 mg $n=33$	Total $N=90$	Placebo $n=25$	Adalimumab 40 mg eow $n=25$	Total $N=50$
Female, n (%)	7 (30.4)	18 (52.9)	13 (39.4)	38 (42.2)	10 (40.0)	9 (36.0)	19 (38.0)
Age (years)							
Mean \pm SD	30.4 \pm 6.9	30.6 \pm 9.3	32.0 \pm 9.6	31.1 \pm 8.8	30.8 \pm 10.9	31.6 \pm 7.2	31.2 \pm 9.2
<30 years	9 (39.1)	15 (44.1)	16 (48.5)	40 (44.4)	11 (44.0)	12 (48.0)	23 (46.0)
Weight (kg)							
Mean \pm SD	56.5 \pm 8.4	55.3 \pm 10.4	54.1 \pm 10.5	55.2 \pm 9.9	56.5 \pm 9.2	58.0 \pm 11.0	57.3 \pm 10.1
Min–Max	43.9–80.3	37.3–80.0	37.0–81.4	37.0–81.4	38.7–74.8	42.1–81.4	38.7–81.4
Tobacco, never used (n , %)	17 (73.9)	19 (55.9)	22 (66.7)	58 (64.4)	11 (44.0)	16 (64.0)	27 (54.0)
Alcohol, non-drinker (n , %)	14 (60.9)	21 (61.8)	24 (72.7)	59 (65.6)	14 (56.0)	15 (60.0)	29 (58.0)
Duration of CD (years)							
Mean \pm SD	7.9 \pm 4.7	9.2 \pm 6.6	11.0 \pm 7.1	9.5 \pm 6.4	8.2 (7.4)	9.9 (5.3)	9.1 (6.4)
Range	0.7–19.2	0.4–27.4	0.3–24.2	0.3–27.4	0.3–27.4	2.4–21.3	0.3–27.4
CDAI score							
Mean \pm SD	308.1 \pm 63.8	302.7 \pm 66.6	300.5 \pm 66.5	303.3 \pm 65.2	296.7 \pm 65.3	325.5 \pm 62.3	311.1 \pm 64.9
Range	221–444	221–448	221–448	221–448	221–448	223–448	221–448
CDAI score (n , %)							
<300	13 (56.5)	19 (55.9)	18 (54.5)	50 (55.6)	13 (52.0)	11 (44.0)	24 (48.0)
≥ 300	10 (43.5)	15 (44.1)	15 (45.5)	40 (44.4)	12 (48.0)	14 (56.0)	26 (52.0)
IOIBD score							
Mean \pm SD	3.7 \pm 1.2	3.4 \pm 1.6	3.3 \pm 1.5	3.4 \pm 1.5	3.2 \pm 1.8	3.1 \pm 1.2	3.2 \pm 1.5
Range	2–7	1–6	1–7	1–7	1–7	1–6	1–7
IBDQ score, Mean \pm SD	139.4 \pm 26.8	148.6 \pm 27.9	145.9 \pm 25.2	145.2 \pm 26.6	151.6 \pm 26.2	144.2 \pm 23.1	147.9 \pm 24.7
SF-36 summary score, Mean \pm SD							
Mental component	39.0 \pm 11.7	39.5 \pm 10.3	38.7 \pm 10.5	39.1 \pm 10.6	41.4 \pm 10.7	38.2 \pm 10.4	39.8 \pm 10.6
Physical component	43.8 \pm 7.6	42.9 \pm 7.8	43.3 \pm 6.3	43.3 \pm 7.2	45.0 \pm 6.5	42.9 \pm 7.7	43.9 \pm 7.1
C-reactive protein (mg/dL), Mean \pm SD	2.5 \pm 2.0	3.0 \pm 2.8	2.2 \pm 2.0	2.6 \pm 2.3	2.6 \pm 2.0	2.2 \pm 1.8	2.4 \pm 2.0

Eow = every other week; CD = Crohn's disease; CDAI = Crohn's disease activity index; IOIBD = International Organization for the Study of Inflammatory Bowel Disease; IBDQ = Inflammatory Bowel Disease Questionnaire; SF-36 = Short Form-36.

^a Baseline is Week 0 of induction trial for both the induction and maintenance trials.

^b Patients enrolled in the induction trial who were randomly assigned to 1 of the 3 treatment groups and received at least 1 dose of study drug.

^c Patients who entered the double-blind portion of the maintenance trial and received at least 1 dose of study drug.

Table 2 Crohn's disease-related medication prior to or at baseline of induction and maintenance trials.^a

Baseline medication use	Induction trial				Maintenance trial		
	Full analysis set ^b				Full analysis set ^c		
	Placebo n=23	Adalimumab 80/40 mg n=34	Adalimumab 160/80 mg n=33	Total N=90	Placebo n=25	Adalimumab 40 mg eow n=25	Total N=50
Aminosalicylates	23 (100)	27 (79.4)	32 (97.0)	82 (91.1)	19 (76.0)	25 (100.0)	44 (88.0)
Immunosuppressants	8 (34.8)	11 (32.4)	10 (30.3)	29 (32.2)	7 (28.0)	11 (44.0)	18 (36.0)
Corticosteroids	5 (21.7)	6 (17.6)	8 (24.2)	19 (21.1)	5 (20.0)	3 (12.0)	8 (16.0)
CD-related antibiotics	2 (8.7)	1 (2.9)	2 (6.1)	5 (5.6)	1 (4.0)	1 (4.0)	2 (4.0)
Enteral nutrition	16 (69.6)	22 (64.7)	23 (69.7)	61 (67.8)	12 (48.0)	17 (68.0)	29 (58.0)
Anti-TNF ^d	13 (56.5)	20 (58.8)	19 (57.6)	52 (57.8)	14 (56.0)	13 (52.0)	27 (54.0)

Data are n (%).

Eow = every other week; CD = Crohn's disease.

^a Baseline is Week 0 of induction trial for both the induction and maintenance trials.

^b Patients enrolled in the induction trial who were randomly assigned to 1 of the 3 treatment groups and received at least 1 dose of study drug.

^c Patients who entered the double-blind portion of the maintenance trial and received at least 1 dose of study drug.

^d Previous use of infliximab or biologic, if any, had to be discontinued at least 8 weeks before Baseline.

differences in Baseline characteristics across treatment groups for either trial.

3.3. Efficacy

3.3.1. Induction trial

Patients who received adalimumab had rapid improvement in disease activity by Week 2, with continued improvement at Week 4 (Fig. 3A). Patients treated with adalimumab 160/80 mg had the highest rate of clinical remission at Week 4, compared with patients treated with adalimumab 80/40 mg or placebo (Fig. 3A). Anti-TNF-naïve patients were more likely to reach remission at Week 4 compared with patients who had prior anti-TNF exposure in all 3 treatment groups (Fig. 3B). Among patients with prior anti-TNF exposure, the clinical remission rate with adalimumab 160/80 mg treatment was more than double than that with adalimumab 80/40 mg treatment (Fig. 3B).

Significantly more patients treated with adalimumab reached CR-100 at Week 4 compared with placebo ($p < 0.05$ for adalimumab 160/80 mg versus placebo and adalimumab 80/40 mg versus placebo) (Fig. 4A). Treatment with adalimumab was effective regardless of previous exposure to anti-TNF agents, although patients who had not been previously treated with anti-TNF therapy were more likely to reach CR-100 than those previously exposed to anti-TNF agents (Fig. 4A). The percentage of patients achieving CR-70 at Week 4 was greater in the adalimumab groups compared with placebo. However, results were significant only in the group treated with adalimumab 160/80 mg ($p = 0.0062$, Fig. 4B). Adalimumab-treated patients who had not received previous anti-TNF therapy were more likely to reach CR-70 (Fig. 4B).

The mean changes in CDAI from Baseline to Week 2 and Week 4 were, respectively, -75.9 and -101.3 in the adalimumab 160/80 mg group, -74.4 and -81.3 in the adalimumab 80/40 mg group, and -27.2 and -37.5 in the placebo group. The mean changes in IOIBD score from Baseline to Week 2 and Week 4 were, respectively, -1.2 and -1.5 in the adalimumab 160/80 mg group, -0.7 and -0.8 in

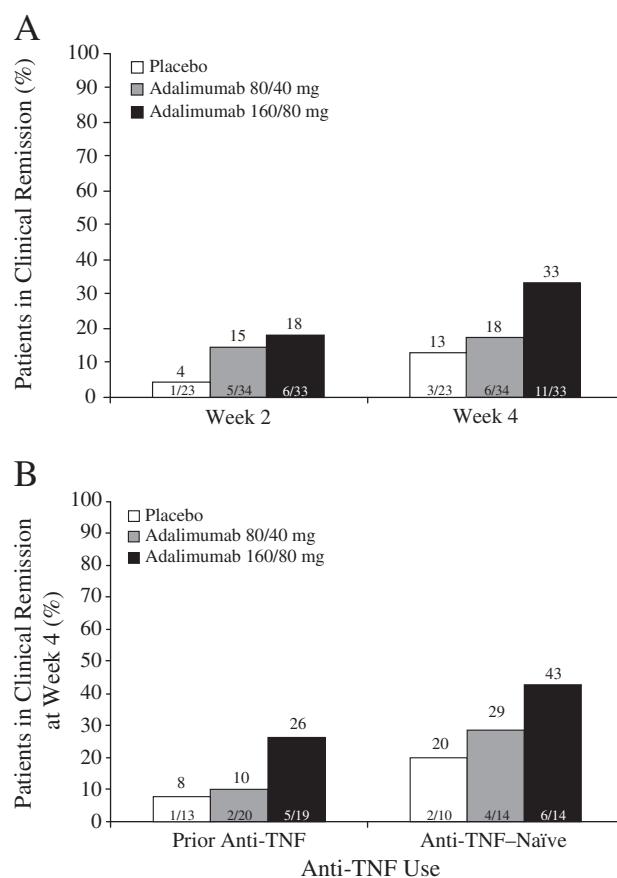


Figure 3 Clinical remission during the induction trial: (A) Remission at Weeks 2 and 4; (B) Remission at Week 4 stratified by prior anti-TNF exposure. Clinical remission is defined as CDAI < 150. Analyses were conducted using non-responder imputation in the FAS (patients who enrolled in the induction trial, were randomly assigned to 1 of the 3 treatment groups and received at least 1 dose of study drug). CDAI = Crohn's disease activity index; FAS = full analysis set.

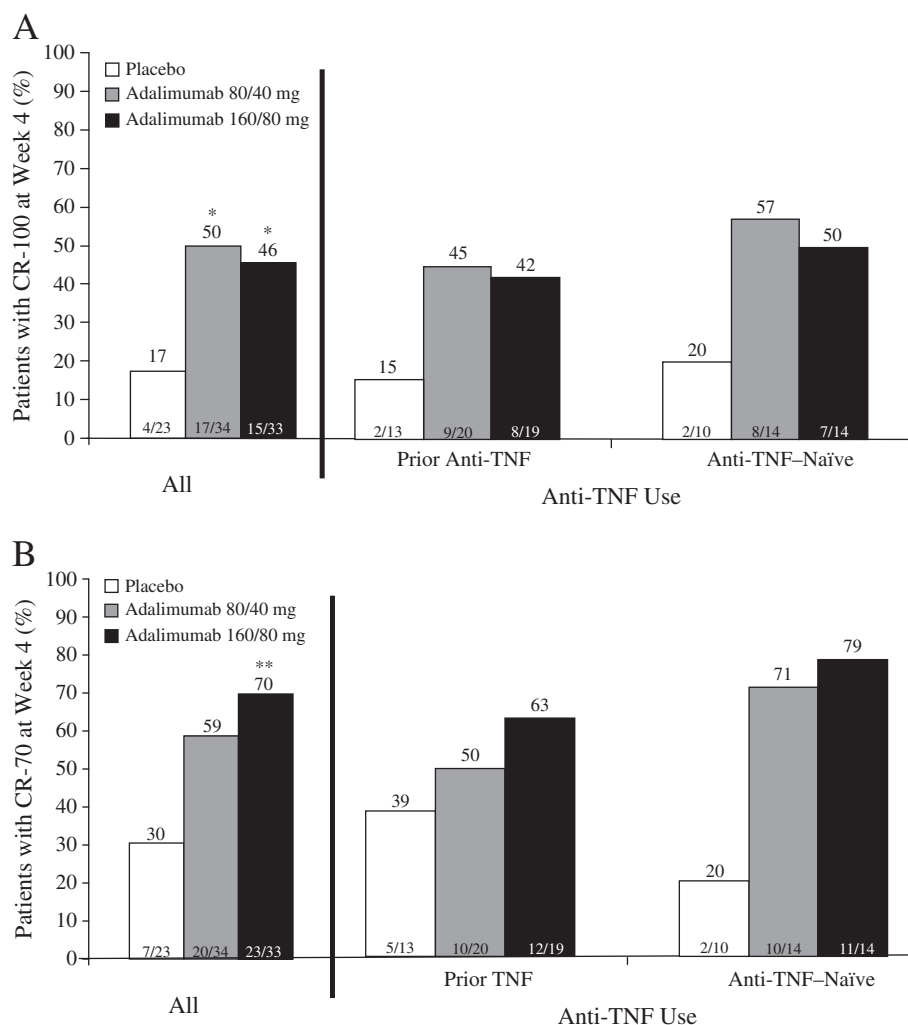


Figure 4 Clinical response during the induction trial: (A) CR-100 at Week 4 [All Patients and Stratified by Prior Anti-TNF Exposure]; (B) CR-70 at Week 4 [All Patients and Stratified by Prior Anti-TNF Exposure]. Analyses were conducted using non-responder imputation in the FAS (patients who enrolled in the induction trial, were randomly assigned to 1 of the 3 treatment groups and received at least 1 dose of study drug). * $p < 0.05$ versus placebo; ** $p = 0.0062$ versus placebo; all other p -values > 0.05 . CR-100 = decrease in CDAI from Baseline ≥ 100 ; CR-70 = decrease in CDAI from Baseline ≥ 70 ; CDAI = Crohn's disease activity index; FAS = full analysis set.

the adalimumab 80/40 mg group and -0.4 and -0.5 in the placebo group.

3.3.2. Maintenance trial

In the mFAS, a significantly greater percentage of adalimumab-treated patients achieved clinical remission at Week 52x compared with placebo ($p < 0.05$, Fig. 5A). Adalimumab therapy was more effective than placebo in maintaining clinical remission, CR-100, and CR-70 over the course of the trial (Fig. 5A–C). Eight (16%) randomized patients (5 placebo-treated and 3 adalimumab-treated) were on corticosteroids when entering the maintenance trial (FAS). Of these, 6 patients (4 placebo-treated and 2 adalimumab-treated) were included in the mFAS population. Among these 6 patients, only 1 (adalimumab-treated) was in steroid-free remission at Week 52x (mFAS). Most of the placebo patients in the double-blind portion (20 of 25) relapsed and switched to open-label adalimumab, whereas

14 out of the 25 adalimumab patients moved from the double-blind portion to the open-label portion (Fig. 2).

In the mFAS, the mean changes (using LOCF) in CDAI from Baseline of the induction trial to Week 0x and 52x were -147.7 and -83.7 in the adalimumab-treated patients and -139.0 and -9.1 in the placebo-treated patients, respectively. The mean changes in IOIBD from Baseline of the induction trial to Week 0x and Week 52x were -2.0 and -0.8 in adalimumab-treated patients and -1.2 and -0.2 in placebo-treated patients, respectively.

The dose escalation set consisted of 30 patients receiving open-label treatment in the maintenance trial for whom the adalimumab dose was increased from 40 mg to 80 mg eow after Week 4x. Within this dose escalation set, 13 patients entered the open-label portion of the maintenance trial at Week 0x and 17 patients moved to the open-label portion after switching from the double-blind portion of the maintenance trial. In the dose escalation set, the percentage of patients who achieved clinical remission, CR-100 or CR-70

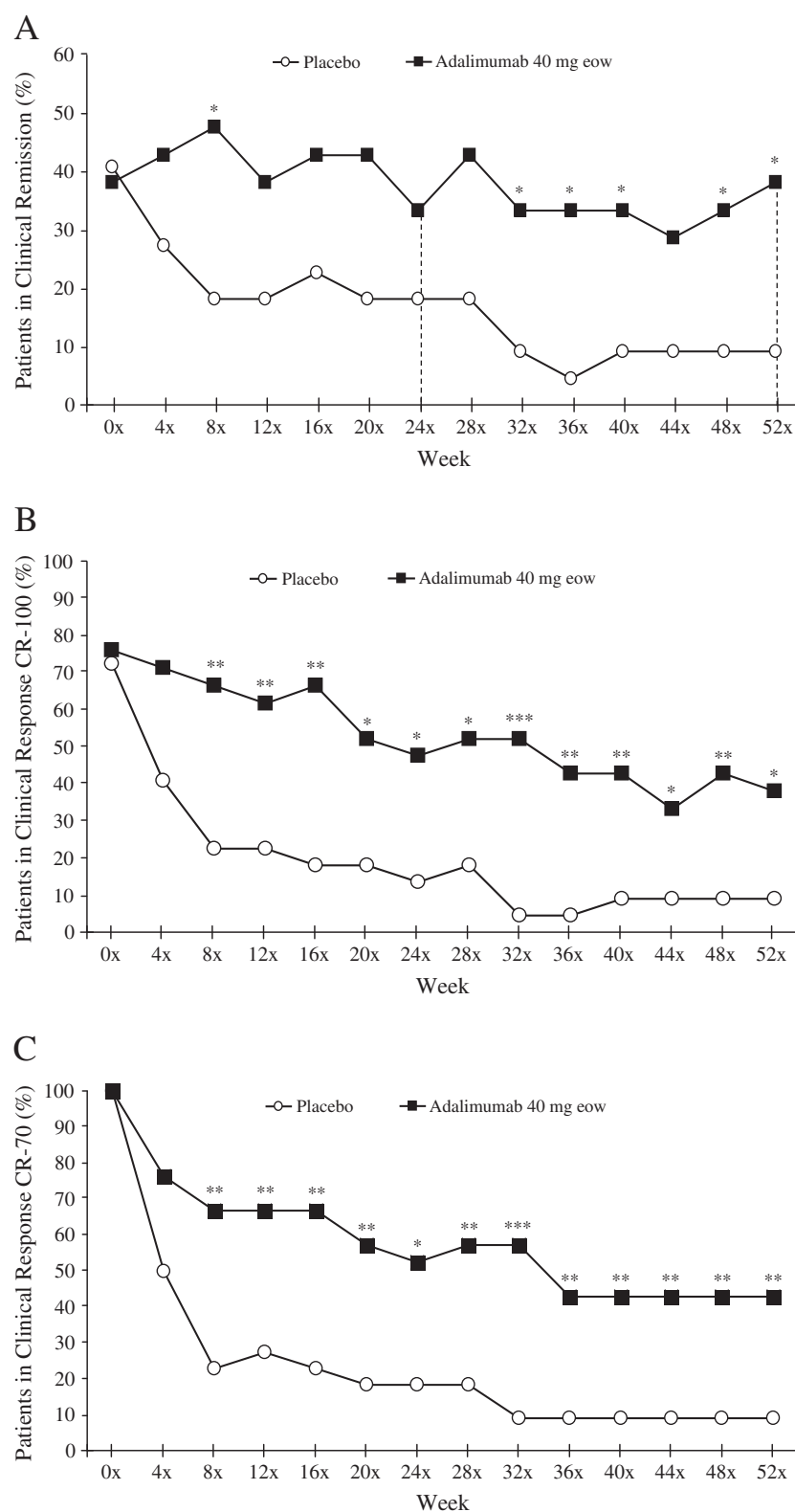


Figure 5 (A) Clinical remission, (B) Clinical response CR-100, and (C) Clinical response CR-70 over time in the maintenance trial. Clinical remission is defined as CDAI < 150. Analyses were conducted using non-responder imputation in the mFAS (patients who received adalimumab in the induction trial, entered the double-blind portion of maintenance trial and received at least 1 dose of study drug); n = 22 for placebo; n = 21 for adalimumab. The "x" beside the week number designates the follow-on nature of the maintenance trial. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; all other p -values > 0.05 . CR-100 = decrease in CDAI from Baseline ≥ 100 ; CR-70 = decrease in CDAI from Baseline ≥ 70 ; CDAI = Crohn's disease activity index; mFAS = modified full analysis set; eow = every other week.

at least once after dose escalation was 20.0%, 40.0%, and 53.3%, respectively. The percentage of patients who showed clinical remission, CR-100 or CR-70 at the time of the last dose was 16.7%, 33.3%, and 40.0%, respectively.

3.4. Quality of life

3.4.1. Induction trial

Induction therapy with adalimumab 160/80 mg or 80/40 mg significantly improved SF-36 MCS from Baseline to Week 4 compared with placebo. The mean change from Baseline for adalimumab 160/80 mg was 6.2 versus -1.6 for placebo ($p=0.0005$); for adalimumab 80/40 mg the mean change from Baseline was 5.5 versus -1.6 for placebo ($p=0.0002$). There was a trend toward a greater improvement in SF-36 PCS and IBDQ for patients in the adalimumab 160/80 mg group compared to placebo, although the changes were not significant

3.4.2. Maintenance trial

In the mFAS, adalimumab 40 mg eow treatment led to significantly greater improvement from Week 0 to Week 8x in SF-36 MCS and IBDQ compared with placebo (12.0 versus 2.0, $p=0.03$ and 34.8 versus 8.3, $p=0.05$, respectively); improvement was sustained. Although the difference between the 2 groups was not statistically significant through Week 52x, the improvement in SF-MCS scores from Week 0 to Week 52x was 9.6 with adalimumab 40 mg eow treatment versus 0.3 for placebo. The improvement in IBDQ from Week 0 to Week 52x was 27.9 for adalimumab-treated patients versus 1.8 for placebo-treated patients. The average IBDQ score at Week 52x for adalimumab-treated patients was 170.1, which is above the threshold of remission (170), whereas the average IBDQ at Week 52x for placebo-treated patients is below the remission threshold (Fig. 6).

SF-36 PCS scores did not differ significantly between the 2 treatment groups at Week 52x. However, from Week 0x through Week 52x, patients treated with adalimumab were

able to maintain the Week 0x improvement of 5.8 while patients treated with placebo showed a decrease in improvement from 2.4 at Week 0x to 0.2 at Week 52x.

3.5. Pharmacokinetics and immunogenicity

Overall, during the induction phase the mean serum adalimumab concentrations from the adalimumab 160/80 mg dose groups were approximately twice those of the adalimumab 80/40 mg group (Fig. 7A). In the maintenance trial, serum concentrations in patients who remained on adalimumab 40 mg eow through Week 52x ($n=15$) remained relatively constant from Week 4x to Week 52x (Fig. 7B–C). Mean serum concentrations tended to increase in patients who increased from adalimumab 40 mg eow to 80 mg eow (Fig. 7B–C).

The overall AAA+ rate was 0% in the induction trial, and 6.1% in the maintenance trial (5 of 82 patients who received at least 1 dose of adalimumab in the trial). In the 5 patients who developed AAA, including 1 patient who increased from adalimumab 40 mg to 80 mg, the serum adalimumab concentrations decreased to below or near detectable limits of the assay by the end of the maintenance trial. Three of the 5 patients discontinued early from the trial due to adverse events (abdominal abscess in 1 patient, liver abscess in 1 patient, aggravation of CD in 1 patient) and 2 patients were not in clinical remission at Week 52x. None of the 5 patients were treated with concomitant immunosuppressant therapy.

3.6. Changes in C-reactive protein

Baseline CRP values from the induction and maintenance trials are reported in Table 1. The mean change in CRP values from Baseline to Week 52x was 0.4 ± 0.7 mg/dL for placebo-treated versus -1.3 ± 1.2 mg/dL for adalimumab-treated patients (mFAS).

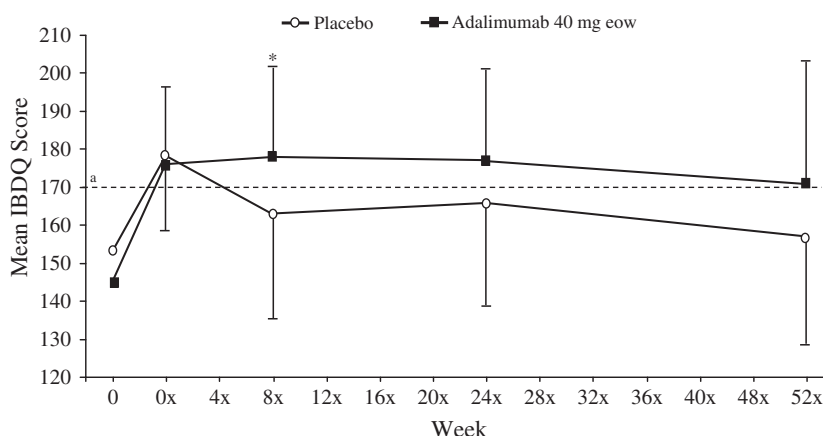


Figure 6 Mean IBDQ scores by week in the maintenance trial. Analyses were conducted using last observation carried forward in the mFAS (patients who received adalimumab in the induction trial, entered the double-blind portion of maintenance trial and received at least 1 dose of study drug); $n=22$ for placebo; $n=21$ for adalimumab. Week 0 is Baseline of the induction trial; Week 0x is Baseline of the maintenance trial; "x" beside the week number designates the follow-on nature of the maintenance trial. * $p=0.05$ versus placebo; all other p -values >0.05 . ^aCutoff point for IBDQ remission (IBDQ score ≥ 170). mFAS=modified full analysis set; eow = every other week; IBDQ = Inflammatory Bowel Disease Questionnaire.

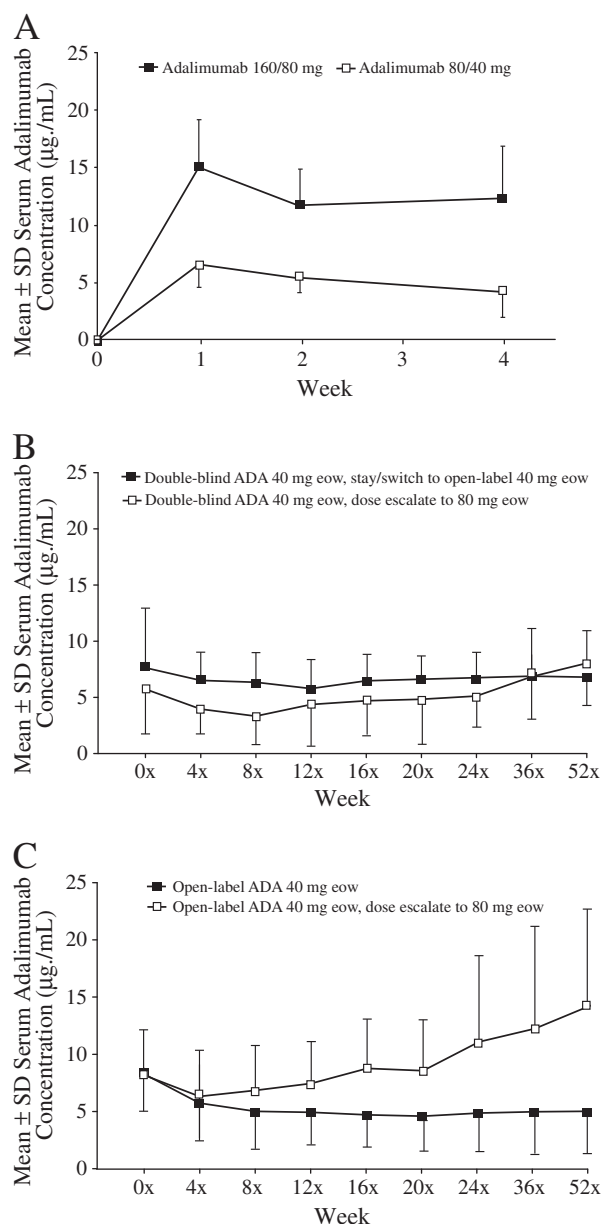


Figure 7 (A) Mean serum adalimumab concentrations in the (A) Induction trial; (B) Double-blind phase of the maintenance trial and (C) Open-label phase of the maintenance trial. Week 0 is Baseline of the induction trial; Week 0x is Baseline of the maintenance trial; “x” beside the week number designates the follow-on nature of the maintenance trial. n=33 for adalimumab 160/80 mg; n=34 for adalimumab 80/40 mg; n=15 for double-blind adalimumab 40 mg eow, stay/switch to open-label adalimumab 40 mg eow; n=10 for double-blind adalimumab 40 mg eow, dose escalate to adalimumab 80 mg eow; n=19 for open-label adalimumab 40 mg eow; n=13 for open-label 40 mg eow, dose escalate to 80 mg eow. ADA = adalimumab; eow = every other week; SD = standard deviation.

3.7. Safety

Serious adverse events (SAEs) were reported in 6.0% of adalimumab-treated patients versus 8.7% in the placebo group of the induction trial (FAS), and 8.0% of adalimumab-

treated patients versus 24.0% in the placebo group of the maintenance trial (FAS) (Table 3). Most SAEs were related to the underlying CD. No deaths, lupus-like syndromes, demyelinating diseases, or cases of tuberculosis were reported in either trial. The incidence of injection site pain was low and similar in all groups in both trials.

4. Discussion

The purpose of the present trials was to demonstrate that efficacy of adalimumab was numerically greater than placebo for the treatment of Japanese patients with CD. Due to the low prevalence of CD in Japan, these trials were of small size, however, were expected to demonstrate similar trends with regard to efficacy and safety of adalimumab as previously shown in Western patients.

Induction treatment with adalimumab increased remission and response rates at Week 4 compared with placebo treatment in Japanese patients with moderate to severe CD. The effect was more pronounced at the higher adalimumab dose (160/80 mg). In Japanese patients previously exposed to anti-TNF, only adalimumab 160/80 mg was able to induce clinical remission at Week 4. The results of this trial are consistent with induction results of adalimumab in Western patients from the CLASSIC I and GAIN clinical trials.^{5,16}

Maintenance treatment with adalimumab increased the clinical remission and response rates at Week 52x compared with placebo treatment in this trial. These results are similar to maintenance results from the CHARM clinical trial.⁹

Only 1 maintenance regimen of adalimumab, 40 mg eow, was tested in a parallel blinded design in the maintenance trial. However, the efficacy of adalimumab 80 mg eow was explored in patients that had an inadequate response to adalimumab 40 mg eow in the open-label portion of the maintenance trial. From the 90 patients included at Week 0 of induction trial, 30 patients subsequently moved to the open-label arm and increased their dose of adalimumab to 80 mg eow, which corresponds to the reported dose-escalation rate of 27% in Western patients.¹⁷ More than half of the Japanese patients who increased to adalimumab 80 mg eow achieved a clinical response CR-70, which is similar to data from Western studies in which 63% of the patients who increased to adalimumab 40 mg weekly dosing achieved CR-70 at any time after dose escalation.¹⁷

Adalimumab therapy resulted in a trend toward an improvement in quality of life, as measured by SF-36 MCS, SF-36 PCS, and IBDQ scores, in Japanese patients evaluated in these trials. The improvement of quality of life was most pronounced for SF-36 MCS and IBDQ scores.

Serum adalimumab concentrations reached a steady state following induction, and remained relatively constant from Week 4x to Week 52x in the maintenance trial, as was previously observed in studies of adalimumab in Western patients with CD.^{5,16} The rate of immunogenicity through 1 year of treatment with adalimumab in the Japanese patients enrolled in these trials (6.1%) was slightly higher than the 2.6% rate observed in the CLASSIC II clinical trial in Western patients with CD.¹⁸ A trend towards a lower plasma level of adalimumab and a higher rate of AAAs in Japanese patients compared with Western patients has already been noted in rheumatoid arthritis.¹⁹ The difference of AAA

Table 3 Treatment-emergent adverse events.^a

	Induction trial			Maintenance trial		Any ADA set ^d
	Full analysis set ^b			Full analysis set ^c		Total N=90
	Placebo n=23	Adalimumab 80/40 mg n=34	Adalimumab 160/80 mg n=33	Placebo n=25	Adalimumab 40 mg eow n=25	
All adverse events	12 (52.2)	20 (58.8)	17 (51.5)	21 (84.0)	20 (80.0)	85 (94.4)
Serious adverse events	2 (8.7)	3 (8.8)	1 (3.0)	6 (24.0)	2 (8.0)	35 (38.9) ^e
Adverse events leading to discontinuation of therapy	1 (4.3)	2 (5.9)	1 (3.0)	6 (24.0)	1 (4.0)	21 (23.3)
Any infection	2 (8.7)	5 (14.7)	4 (12.1)	9 (36.0)	15 (60.0)	65 (72.2)
Serious infection	0 (0.0)	1 (2.9) ^f	0 (0.0)	2 (8.0)	1 (4.0)	6 (6.7)
Malignant adverse events	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Injection-site-related pain	2 (8.7)	5 (14.7)	4 (12.1)	1 (4.0)	2 (8.0)	16 (17.8)
Related opportunistic infections (excluding tuberculosis)	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.1)
Related congestive heart failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Demyelinating disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tuberculosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Related allergic reactions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)
Lupus-like syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data are n (%).

ADA = adalimumab; eow = every other week.

^a In the induction and maintenance trials, a treatment-emergent AE (TEAE) was defined as any AE with onset from 1st dose of study drug, with differing end points depending on whether the patient continued in the adalimumab development program or not. Specifically, for patients who continued in the adalimumab development program, the end-date for reporting TEAEs was at the trial end (Week 4 or 8 for induction trial; Week 52x for maintenance trial); for patients who discontinued the trial and did not continue in adalimumab development program, the end-date for reporting TEAEs was up to 70 days following the last study drug administration. For analysis in the any adalimumab set (combines induction and maintenance trial), a TEAE was defined as any AE with onset from 1st dose of adalimumab the patient ever received (which could have been in the induction trial for those randomized to adalimumab, or in the maintenance trial for those randomized to placebo in the induction trial) through an end-date up to the last dose received in the maintenance trial if the patient continued after Week 52x, or up to 70 days after the last dose of adalimumab if the patient discontinued either trial. Of note, for the any adalimumab set, events that occurred during the placebo period prior to receipt of any adalimumab were excluded.

^b Patients enrolled in the induction trial who were randomly assigned to 1 of the 3 treatment groups and received at least 1 dose of study drug.

^c Patients who entered the double-blind portion of the maintenance trial and received at least 1 dose of study drug.

^d Patients who received at least 1 dose of adalimumab either, in the induction trial or, in the maintenance trial.

^e SAEs included: 6 SAEs occurred in ≥ 2 patients, aggravation of Crohn's disease (20 patients), abdominal abscess (5 patients), ileus (2 patients), intestinal obstruction (2 patients), peritonitis (2 patients) malnutrition (2 patients). No SAE of malignancy, demyelinating disorder, tuberculosis was reported.

^f Abdominal abscess developed 25 days after the last dose of study drug, considered by the investigator to be probably not related to adalimumab.

production between Japanese and Western patients may relate to the different distribution in the IgG1 allotype GM1^{2a} across racial groups; 84% of Japanese carry the allotype GM1^{2a}, compared with only 29% of Western Europeans. Circulating adalimumab, which is an IgG1 GM1^{2a}, may reach a more optimal integration into the immunoregulatory network in GM1^{2a}-carrying patients, and cause a higher rate of physiological anti-idiotypic antibodies.²⁰

Adalimumab therapy was well-tolerated, and no deaths were reported in either the induction or maintenance trial. Adverse event profiles were similar to those reported in other clinical trials of adalimumab in Western patients with CD.

The similarity of the clinical remission and response rates in these small trials to the results of larger pivotal clinical trials of adalimumab in CD supports the use of

adalimumab for induction and maintenance of remission in Japanese patients with moderate to severely active CD. However, because of the limited number of patients enrolled, these trials lacked statistical power to conclusively demonstrate the efficacy of adalimumab in this population. A further limitation of these trials was the exclusion of patients who had previously been exposed to but had failed to respond to infliximab (primary non-responders). The response of such Japanese patients to adalimumab treatment cannot be estimated from the results. Nevertheless, the results of these 2 trials in Japanese patients with CD are consistent with results reported in prior clinical trials of adalimumab. Our findings show that adalimumab is an effective and well-tolerated therapeutic option for inducing and maintaining clinical remission of moderate to severe CD in this population.

Conflict of interest statement

Disclosures of financial conflict of interest are summarized below:

- M Watanabe: Consulting and/or other fees from Abbott Japan, Ajinomoto Pharma, Asahi Kasei Kurary Medical, Eisai, JIMRO, Kyorin Pharmaceutical, Mitsubishi Tanabe Pharma, Otsuka Pharmaceutical, UCB Japan, ZERIA Pharmaceutical
- T Hibi: Consulting and/or other fees from Abbott Japan, Ajinomoto Pharma, Asahi Kasei Kurary Medical, AstraZeneca, Eisai, Janssen, JIMRO, Kyorin Pharmaceutical, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Otsuka Pharmaceutical, UCB Japan, ZERIA Pharmaceutical
- KG Lomax: Employee of Abbott
- SK Paulson: Employee of Abbott
- J Chao: Employee of Abbott
- MS Alam: Former employee of Abbott
- A Camez: Employee of Abbott.

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analyzed the data and helped draft the manuscript. SKP analyzed the data and helped draft the manuscript. JC analyzed the data and helped draft the manuscript. MSA participated in the study design, analyzed the data, and helped draft the manuscript. AC participated in the study design, carried out the studies, analyzed and reported the data, and helped draft the manuscript. All authors read and approved the final manuscript.

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