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ORIGINAL ARTICLE

Phase III, multicenter, open-label, long-term study of the safety of abatacept in Japanese patients with rheumatoid arthritis and an inadequate response to conventional or biologic disease-modifying antirheumatic drugs

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Abstract

Objectives. To examine the long-term safety of intravenous (IV) abatacept treatment in Japanese patients with rheumatoid arthritis (RA) and an inadequate response to methotrexate (MTX) or other conventional or biologic disease-modifying antirheumatic drugs.

Methods. This Phase III, open-label, long-term study (NCT00484289) comprised Japanese patients with RA who had completed abatacept Phase I or Phase II studies, and new patients intolerant to MTX. Patients from Phase I and Phase II studies received a weight-tiered dosing equivalent of 10 mg/kg abatacept, with MTX at doses up to 8 mg/week; newly enrolled patients received weight-tiered 10 mg/kg abatacept monotherapy. Safety and efficacy were assessed.

Results. A total of 217 patients (Phase I, $n = 13$; Phase II, $n = 178$; newly enrolled, $n = 26$) were treated with IV abatacept for a mean of 3 years. Serious adverse events occurred in 67/217 (30.9%) patients. Most adverse events were mild or moderate. For all cohorts combined, American College of Rheumatology 20% response rates ranged from 61.3 to 81.8% for as-observed and last observation carried forward analyses over 192 weeks. Following initial response, clinical and functional outcomes were maintained for up to 3 years.

Conclusions. In Japanese patients with RA, IV abatacept with and without background MTX showed tolerable safety and sustained efficacy over 3 years.

Keywords

abatacept, Japanese, long-term study, rheumatoid arthritis

History

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Introduction

Chronic diseases such as rheumatoid arthritis (RA) require treatments that provide durable efficacy, and which are safe and well tolerated over the long term. While the majority of Japanese patients with RA start their treatment with a conventional disease-modifying antirheumatic drug (DMARD) such as methotrexate (MTX) [1], some patients do not achieve adequate clinical benefit with MTX and may experience serious adverse events such as liver toxicity and bone marrow suppression [2]. Furthermore, MTX should not be administered to some patients due to safety concerns, such as a history of liver or kidney disorders [3]. As many such patients have significant disease activity, additional therapeutic options are necessary. Biologic DMARD therapies for RA provide increased clinical and structural benefit compared with conventional DMARDs [4,5]. First approved more than a decade ago [6], a variety of biologic agents with differing mechanisms of action are currently available.

Abatacept is a fully humanized, soluble, recombinant fusion protein consisting of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and the Fc domain of human immunoglobulin (Ig) G1. It is the only treatment for RA that mimics the naturally occurring homeostatic mechanism of human CTLA-4 and inhibits the interaction of CD28 with CD80/86 on the antigen-presenting cell, thus selectively modulating the co-stimulatory signal required for full T-cell activation [7].

The safety and efficacy of intravenous (IV) abatacept has been well established in the global population, with both short-term and long-term studies. IV abatacept is currently approved in the USA, the European Union, Japan, and several other countries for the treatment of moderate-to-severe RA, and a subcutaneous formulation is becoming more widely available worldwide. The IV formulation of abatacept is effective, with favorable safety, in patients with RA who are MTX-naïve [8], MTX inadequate responders [9,10], or anti-tumor necrosis factor inadequate responders [11].

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IV abatacept has demonstrated favorable tolerability and clinical efficacy benefits among Japanese patients with RA who are MTX inadequate responders [12]. The safety, tolerability, pharmacokinetics, immunogenicity, and preliminary evaluations of the efficacy and pharmacodynamics of abatacept (2, 8, and 16 mg/kg) were examined in a Phase I, multicenter, open-label, dose-escalation study in Japanese patients with RA ($n = 21$; IM101-034) [13]. Abatacept had favorable safety and was well tolerated up to the highest dose of 16 mg/kg over 57–127 days, and pharmacokinetic outcomes were similar to those reported in another open-label clinical study of IV abatacept [14]. Abatacept was found to be effective (as assessed by American College of Rheumatology 20% [ACR20] response) in patients in each of the three dose groups. A Phase II study (IM101-071, NCT00345748) examined the dose response of abatacept (2 and 10 mg/kg) compared with that of placebo and background MTX in Japanese patients with active RA over 24 weeks ($n = 195$) [12]. This study demonstrated significantly greater ACR20, ACR50, and ACR70 responses with abatacept 10 mg/kg compared to those with placebo ($P < 0.0001$), whereas smaller but statistically significant responses were seen in the 2 mg/kg abatacept group. Additionally, abatacept plus MTX was found to be well tolerated.

The primary objective of the present 3-year, long-term study (ClinicalTrials.gov identifier NCT00484289) was to examine the safety of continuous IV abatacept in patients with RA who participated in either the Phase I or the Phase II studies, or were newly enrolled and received abatacept monotherapy due to the inability to tolerate MTX owing to safety concerns and had an inadequate response to other DMARDs. The secondary objectives of this study included assessment of clinical and functional efficacy, health-related quality of life, immunogenicity, and laboratory and pharmacodynamic outcomes.

Patients and methods

Patient population

This study comprised three cohorts of patients with RA, including patients who previously participated in either the Japanese Phase I study IM101-034 (February 2004–December 2005) or the Japanese Phase II study IM101-071 (June 2006–November 2007), or new patients enrolling in this study who were MTX-intolerant, had never received abatacept before, and had an inadequate response to DMARDs other than MTX, including biologics. Each cohort consisted of Japanese males and females aged ≥ 20 years with a diagnosis of RA as defined by the American Rheumatism Association (1987) [15] and an ACR functional status of Class I, Class II or Class III [16]. Further eligibility criteria applied to the particular cohorts are described below.

In the Phase I, open-label, dose-escalation study, patients who had been receiving DMARDs at registration were treated with single or multiple doses (Days 1, 15, 29, and 57) of IV abatacept 2, 8, or 16 mg/kg [13]. Patients who were withdrawn from the Phase I study due to safety reasons were excluded from this Phase III study. Between Phase I and Phase III, patients may have been treated with other biologic agents. At registration for this Phase III study, patients from Phase I were required to have undergone the following washout periods: infliximab discontinuation at least 56 days prior to screening and 84 days prior to the first administration of abatacept, and etanercept withdrawal at least 28 days prior to screening.

In the Phase II study, patients with active RA and an inadequate response to MTX were treated with IV abatacept 2 or 10 mg/kg plus MTX, or placebo plus MTX, for 24 weeks [12]. Patients from Phase II must have completed the IM101-071 study to be eligible for the present Phase III study. Additionally, patients from Phase II could not have received any biologics between the completion of IM101-071 and enrollment in the Phase III study.

The new patient cohort with MTX intolerance consisted of patients who could not receive MTX owing to safety reasons. These patients presented with an inadequate response to conventional DMARDs or biologics, and had ≥ 6 swollen joints and ≥ 8 tender joints at the time of screening. In this new patient cohort, infliximab, and etanercept were discontinued as described above for patients from Phase I, and DMARDs were withdrawn at least 28 days prior to screening.

Exclusion criteria for all three cohorts in the current Phase III study included those patients who, at screening, had received unlicensed biologics (excluding abatacept) from previous or ongoing studies in Japan. Additionally, patients who had received any investigational drug (excluding abatacept) within five half-lives of the product or 56 days before screening were excluded. Patients were also excluded if they were currently under treatment with leflunomide, mycophenolate mofetil, calcineurin inhibitors such as cyclosporine and tacrolimus, D-penicillamine, cyclophosphamide, or immunoadsorption columns at screening.

Study design

This was a multicenter, open-label, long-term study that was conducted at 40 sites in Japan. The study was therefore performed in an open-label and uncontrolled manner and no hypotheses were planned. The study was planned to continue until the approval of IV abatacept in Japan, and thus, a specific duration of administration of abatacept was not set. The protocol and patients' informed consent received institutional review board/independent ethics committee approval; the study was conducted in accordance with the Declaration of Helsinki and was consistent with Good Clinical Practice guidelines of the International Conference on Harmonisation.

All patients, regardless of previously received abatacept dose (from Phases I and II), were given abatacept at a weight-tiered dose approximating 10 mg/kg (500 mg for patients weighing < 60 kg, 750 mg for patients weighing 60–100 kg, and 1 g for patients weighing > 100 kg). The dose was administered intravenously at Weeks 0, 2, 4, and every 4 weeks thereafter. From the second year of participation in the study, patients were reweighed once a year and their abatacept dose was checked and adjusted if needed. Concomitant administration of other biologics was prohibited in all patients. New patients with MTX intolerance were not permitted to use concomitant conventional DMARDs during the first 12 weeks, whereas patients enrolled from the Phase I and Phase II studies were permitted to use conventional DMARDs (MTX, < 8 mg/week) from the time of enrollment. In addition, use of corticosteroids (total dose, ≤ 10 mg/day prednisolone equivalent) and non-steroidal anti-inflammatory drugs were permitted in all patients. Patients who discontinued from the study were followed up at the time of discontinuation and for 12 weeks following the last abatacept administration.

Safety assessments

Adverse events (AEs), serious adverse events (SAEs), and laboratory tests were recorded throughout the study. An AE was defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a patient administered abatacept that did not necessarily have a causal relationship with treatment. An SAE was defined as any AE that resulted in death, disability, or hospitalization, or that was life-threatening. If a patient experienced an AE during the study, abatacept was continued only if the AE resolved and was considered not clinically significant.

Laboratory tests included hematology, blood chemistry, and urinalysis. "Abnormal laboratory values" were defined as values that deviated from the normal range defined by the central laboratory. Average changes in laboratory tests were calculated based on the normal ranges in females. Supplementary Tables 1 and 2 available online at: http//informahealthcare.com/doi/abs/10.3109/14397595.2014.899179 show definitions of severity for AEs and criteria for selecting abnormal laboratory values, respectively.

Immunogenicity and pharmacodynamic assessments

Immunogenicity was assessed based on the levels of anti-abatacept (CTLA-4-Ig) antibodies and anti-CTLA-4 antibodies (CTLA-4-T: CTLA-4 without the Ig region) in blood using an enzyme-linked immunosorbent assay (ELISA). Blood samples were collected for immunogenicity assessments prior to abatacept administration at Week 0 and every 24 weeks thereafter. If a patient discontinued the study prematurely, immunogenicity was assessed at discontinuation and at 4, 8, and 12 weeks after the final administration of abatacept. When the serum concentration of abatacept was <1 μg/mL, seropositive samples with anti-CTLA-4-T reactivity were further characterized using a cell-based neutralization assay to determine whether the sample had neutralizing antibody activity.

Rheumatoid factor (RF) and C-reactive protein (CRP) concentration levels were measured as pharmacodynamic parameters. Samples for the assessment of RF concentration levels were taken at Week 0 and every 12 weeks thereafter. Samples for the assessment of CRP concentration levels were taken at Weeks 0, 2, and 4, and then every 4 weeks for the first year, followed by every 12 weeks for the remainder of the study.

Efficacy assessments

Clinical efficacy was evaluated by ACR20, ACR50, and ACR70 responses [17]. Disease activity was measured by the rates of patients achieving a low disease activity state (LDAS; 28-joint Disease Activity Score [DAS28] [CRP] of ≤ 3.2) and remission (DAS28 [CRP] of <2.6). Physical function was measured by patient-reported Health Assessment Questionnaire (HAQ) response (improvement from baseline of ≥ 0.3 units) [18]. The above efficacy assessments were made at Week 0 and every 12 weeks thereafter. Health-related quality of life was assessed using the Short Form-36 (SF-36) questionnaire at Week 0, and then every 12 weeks for the first year, followed by every 24 weeks for the remainder of the study.

Statistical analysis

Data are presented for the pooled population and by original cohort. All patients who received at least one infusion of abatacept were included in the safety and efficacy data sets. Patients who discontinued from the study without receiving abatacept were deemed pretreatment dropouts. While there was no hypothesis testing and no power consideration for safety or efficacy, administration of abatacept to 180 patients provided a 95% probability of observing at least one occurrence of any AE that would occur with $\geq 1.7\%$ incidence in the population from which the sample is drawn. All available data from patients who had received abatacept, and for whom baseline and at least one additional measurement had been available, were included in the pharmacodynamic and immunogenicity data sets. Baseline for all patient cohorts was defined as pre-dose of Day 1 for this Phase III study.

Safety data (all AEs) were described and analyzed as frequency distributions. Laboratory test results were summarized using descriptive statistics, and the rate of positive response was calculated for immunogenicity. For pharmacodynamic parameters, concentration levels and changes from baseline were evaluated using descriptive statistics.

All clinical variables, including ACR20/50/70, DAS28 (CRP)-defined LDAS and remission, and HAQ response, were summarized as observed for patients with data available at the visit of interest, using descriptive statistics. In addition to these analyses, a *post hoc* analysis of clinical results (ACR20/50/70, DAS28 [CRP]-defined LDAS and remission, and HAQ response) was carried out using a last observation carried forward (LOCF) analysis. Changes from baseline in each item of the SF-36 were summarized using descriptive statistics.

Results

Patient demographics

Patients completed screening in March 2008; the last day of observation occurred in December 2010. Patient disposition is summarized in Figure 1. A total of 217 patients were treated with abatacept (patients from Phase I, $n=13$; patients from Phase II, $n=178$; new patients with MTX intolerance, $n=26$). Of the 217 patients, 56 (25.8%) discontinued from the study. Reasons for discontinuation included AEs and abnormal laboratory changes (24/217; 11.1%), patient request (13/217; 6.0%), inadequate response (13/217; 6.0%), and other reasons (6/217; 2.8%).

The mean age and weight of patients were 53.8 years and 56.5 kg, respectively, and the majority of patients were female (177/217; 81.6%). Patients had a mean disease duration of 9.1 years at the start of the Phase III study (baseline). The majority (141/217; 65.0%) of patients in each cohort were classified as RA Functional Class II. RA disease activity, as measured by tender joints, swollen joint counts, and CRP levels, was highest in the cohort of new patients with MTX intolerance (Table 1).

While there was at least a 1-year gap between the last day of observation in the Phase I study and the initiation of this Phase III study, there was a median (range) transition period of 12.1 (7.1–25.1) weeks between the final dose of abatacept or placebo in the Phase II study and the first dose of abatacept in the present Phase III study. Following this Phase II to Phase III transition period, patients from Phase II had a median (range) duration of exposure to abatacept of 37.7 (3.6–45.1) months. The median (range) duration of exposure to abatacept in patients from Phase I was 42.4 (31.3–44.0) months, 32.3 (1.0–44.0) months in new patients with MTX intolerance, and 37.7 (1.0–45.1) months in all patients combined. More than half (126/217; 58.1%) of all patients were treated with abatacept for more than 3 years. One abatacept infusion was missed in 34/217 (15.7%) patients during the present treatment period; however, no patients had missed more than two consecutive doses. Seven patients missed three or more doses in total; in all the cases, the reason for missing the dose was an AE.

At the time of enrollment, most patients were receiving concomitant MTX therapy (Table 1). MTX dosage (mean [standard deviation, SD]) was 7.11 (1.45) mg/week in patients from Phase I, and 7.11 (1.07) mg/week in patients from Phase II. Concomitant DMARD therapy was prohibited in new patients with MTX intolerance from the start of the study until the completion of Week 12. Concomitant oral corticosteroid therapy (prednisolone: mean [SD] dose, 5.85 [2.41] mg/day in all cohorts) was used by 182/217 (83.9%) patients in the study.

Safety

Adverse events

The overall safety profile for abatacept in all three patient cohorts is shown in Table 2. The most common AEs were

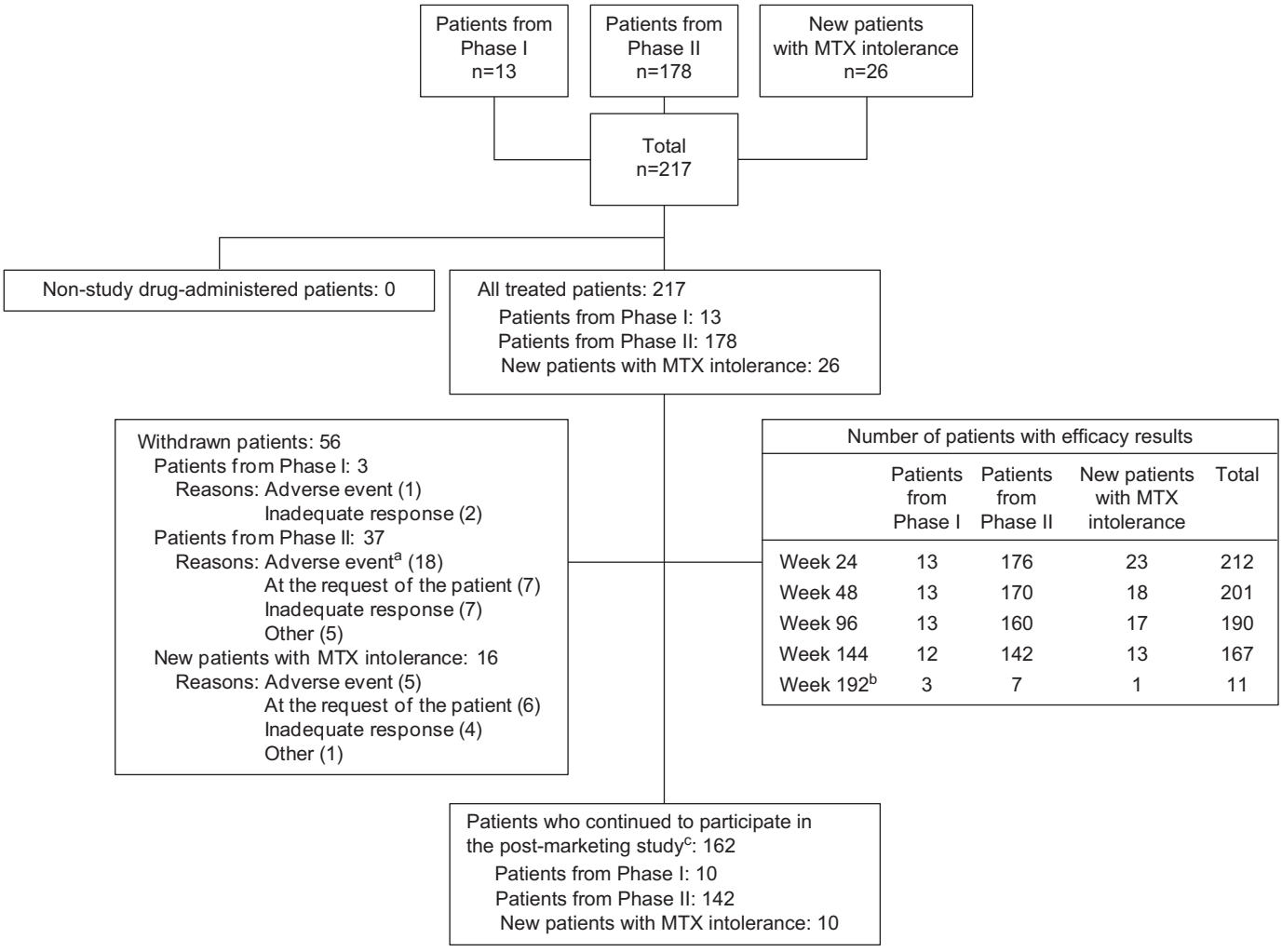

Figure 1. Patient disposition.[a]Discontinuations from adverse events included one discontinuation due to abnormal laboratory changes. [b]Only 11 patients had 192 weeks of treatment at the time of analysis, due to differential enrollment times.[c]The last time point for the study was 27 December 2010, at which point the median (range) cumulative duration of abatacept exposure in all patients combined was 37.7 (1.0–45.1) months. MTX, methotrexate.

Table 1. Patient characteristics.

Variables	Patients from Phase I, $n = 13$	Patients from Phase II, $n = 178$	New patients with MTX intolerance, $n = 26$	Total, $N = 217$
Age (years), mean (SD)	52.8 (11.6)	53.2 (11.5)	57.8 (10.6)	53.8 (11.4)
Weight (kg), mean (SD)	55.2 (9.7)	56.9 (9.4)	53.9 (10.8)	56.5 (9.6)
Number of females, *n* (%)	12 (92.3)	146 (82.0)	19 (73.1)	177 (81.6)
Duration of RA (years), mean (SD)	14.4 (9.0)	8.4 (7.3)	10.9 (10.1)	9.1 (7.9)
Tender joints, mean (SD)	8.4 (5.2)	14.3 (11.2)	22.7 (13.3)	14.9 (11.6)
Swollen joints, mean (SD)	9.1 (4.7)	11.6 (8.7)	17.2 (10.0)	12.1 (8.9)
Pain (VAS 100 mm), mean (SD)	43.1 (23.5)	52.3 (24.9)	80.6 (20.1)	55.1 (26.0)
Physical function (HAQ score), mean (SD)	0.98 (0.57)	1.16 (0.75)	1.80 (0.90)	1.22 (0.79)
Subject Global Assessment (VAS 100 mm), mean (SD)	47.1 (20.7)	50.8 (23.8)	77.3 (20.4)	53.7 (24.8)
Physician Global Assessment (VAS 100 mm), mean (SD)	56.5 (24.7)	47.5 (24.0)	75.5 (16.5)	51.4 (24.9)
CRP (mg/dL), mean (SD)	1.84 (2.84)	2.32 (2.18)	4.67 (3.65)	2.57 (2.55)
Rheumatoid factor (IU/mL)				
Negative (≤ 20), *n* (%)	1 (7.7)	24 (13.5)	4 (15.4)	29 (13.4)
Positive (> 20), *n* (%)	12 (92.3)	154 (86.5)	22 (84.6)	188 (86.6)
DAS28 (CRP), *n*	13	176	21	210
Mean (SD)	4.4 (1.0)	4.8 (1.4)	6.3 (1.0)	5.0 (1.4)
Prior MTX use, *n* (%)	9 (69.2)	178 (100.0)	26 (100.0)	213 (98.2)
Prior conventional DMARD use,[a]*n* (%)	3 (23.1)	6 (3.4)	9 (34.6)	18 (8.3)
Prior biologic use, *n* (%)	9 (69.2)	52 (29.2)	14 (53.8)	75 (34.6)
Concomitant MTX use at registration, *n* (%)	9 (69.2)	175 (98.3)	0	184 (84.8)
Dose (mg/week), mean (SD)	7.11 (1.45)	7.11 (1.07)	–	7.11 (1.09)
Concomitant oral corticosteroid use at registration, *n* (%)	13 (100.0)	146 (82.0)	23 (88.5)	182 (83.9)
Dose (mg/day), mean (SD)	6.15 (2.37)	5.67 (2.38)	6.78 (2.48)	5.85 (2.41)

CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; MTX, methotrexate; RA, rheumatoid arthritis; SD, standard deviation; VAS, visual analog scale.
[a]Other than MTX.

Table 2. Adverse events and serious adverse events.

	Number of patients (%)			
	Patients from Phase I, $n = 13$	Patients from Phase II, $n = 178$	New patients with MTX intolerance, $n = 26$	Total, $N = 217$
AEs	13 (100.0)	176 (98.9)	24 (92.3)	213 (98.2)
Drug-related AEs	13 (100.0)	165 (92.7)	24 (92.3)	202 (93.1)
Discontinuation due to AEs	1 (7.7)	17 (9.6)	5 (19.2)	23 (10.6)
Infections and infestations	11 (84.6)	141 (79.2)	16 (61.5)	168 (77.4)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	22 (12.4)	2 (7.7)	24 (11.1)
Autoimmune disorders	0	7 (3.9)	1 (3.8)	8 (3.7)
Peri-infusional	9 (69.2)	78 (43.8)	16 (61.5)	103 (47.5)
SAEs	4 (30.8)	50 (28.1)	13 (50.0)	67 (30.9)
Drug-related SAEs	2 (15.4)	26 (14.6)	8 (30.8)	36 (16.6)
Discontinuation due to SAEs	0	14 (7.9)	5 (19.2)	19 (8.8)
Infections and infestations	2 (15.4)	11 (6.2)	3 (11.5)	16 (7.4)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	10 (5.6)	1 (3.8)	11 (5.1)
Abnormal laboratory changes	7 (53.8)	125 (70.2)	19 (73.1)	151 (69.6)
Drug-related abnormal laboratory changes	6 (46.2)	102 (57.3)	13 (50.0)	121 (55.8)
Discontinuation due to abnormal laboratory changes	0	1 (0.6)	0	1 (0.5)
Serious abnormal laboratory changes	0	0	1 (3.8)	1 (0.5)
Drug-related serious abnormal laboratory changes	0	0	1 (3.8)	1 (0.5)
Discontinuation due to serious abnormal laboratory changes[a]	0	0	0	0
Deaths	0	1 (0.6)	0	1 (0.5)

AE, adverse event; SAE, serious adverse event; MTX, methotrexate

[a]There were no serious abnormal laboratory changes that led to discontinuation.

nasopharyngitis (123/217 patients, 56.7%), stomatitis (53/217 patients, 24.4%), increased blood pressure (41/217 patients, 18.9%), upper respiratory tract inflammation (35/217 patients, 16.1%), and eczema (32/217 patients, 14.7%). The majority of AEs were mild or moderate. Severe and very severe AEs occurred in 38/217 (17.5%) and in 3/217 (1.4%) treated patients, respectively; AEs classified as very severe are discussed in further detail below under SAEs. AEs (including SAEs) leading to discontinuation occurred in 23/217 (10.6%) treated patients (Table 2). One (1/217; 0.5%) patient from the Phase II study died due to pancreatic carcinoma (Table 2), which is discussed further below. No deaths were reported in the other two cohorts.

Serious adverse events

For the 67/217 (30.9%) patients who reported SAEs (Table 2), all SAEs resolved with appropriate treatment or follow-up except for pancreatic carcinoma, pinealoma/hydrocephalus, thalamus hemorrhage, cerebral infarction, spinal compression fracture, endometrial cancer, pneumonia, and diffuse large B-cell lymphoma occurring in one patient each. The pancreatic carcinoma, thalamus hemorrhage, and a case of sepsis (one patient; 0.5%) were classified as very severe. Sepsis and pancreatic carcinoma were classified as related to study drug, and thalamus hemorrhage was classified as unrelated to study drug. All three of these events resulted in discontinuation, and the SAE of pancreatic cancer, which developed approximately 20 months following the initiation of abatacept treatment, resulted in the one death during the study period.

Overall, SAEs led to discontinuation in 19/217 (8.8%) treated patients (Table 2). In addition to those events mentioned above, patients discontinued due to one or more of the following: cerebral infarction (2/217 patients; 0.9%), cardiac failure, atrial fibrillation, mitral valve incompetence, inflammatory bowel disease, osteomyelitis, subcutaneous abscess, pharyngeal abscess, B-cell lymphoma, breast cancer, diffuse large B-cell lymphoma, endometrial cancer, gastric cancer, pinealoma, T-cell lymphoma, cervix carcinoma stage 0, cerebral hemorrhage, encephalitis, seventh cranial nerve paralysis, and interstitial lung disease (one patient each; 0.5%). One case of cerebral infarction and the SAEs of sepsis, encephalitis, and pharyngeal abscess all occurred in a single patient, resulting in that patient's discontinuation. Similarly, the SAEs of atrial fibrillation, cardiac failure, and mitral valve incompetence occurred in a single patient, resulting in that patient's discontinuation. Interstitial lung disease and the cranial nerve paralysis were classified as unrelated to study drug, and the other events were classified as related by the study investigators.

Laboratory changes

Of the 217 patients treated with abatacept, AEs of abnormal laboratory changes occurred in 151 (69.6%) patients (Table 2). Decreased lymphocyte count ($< 750/\mu L$) was the most common abnormal laboratory change and was reported in 41/217 (18.9%) patients; 34/217 (15.7%) patients exhibited decreased lymphocyte counts classified as related to study drug. Other abnormal laboratory changes (see Supplementary Table 1 available online at: http//informahealthcare.com/doi/abs/10.3109/14397595.2014.899179 for definitions) that occurred in at least 5% of treated patients were as follows: increased white blood cell count (37/217; 17.1%), increased alanine aminotransferase (33/217; 15.2%), increased aspartate aminotransferase (25/217; 11.5%), white blood cells in urine (24/217; 11.1%), increased gamma-glutamyltransferase (16/217; 7.4%), blood present in urine (16/217; 7.4%), red blood cells in urine (16/217; 7.4%), increased eosinophil count (13/217; 6.0%), increased blood glucose (13/217; 6.0%), and glucose present in urine (13/217; 6.0%); none were classified as serious.

Only one patient (1/217; 0.5%) had an abnormal laboratory change (increased CRP) that was classified as serious (Table 2). This patient also had a high white blood cell count, leading study investigators to suspect that these changes occurred due to infection; however, the causative pathogen could not be identified and the patient was discharged when the symptoms resolved. One patient from Phase II, who tested positive for hepatitis B surface antigens, had an abnormal laboratory change that led to discontinuation of study treatment (1/217; 0.5%). This event, which was classified as "possibly" related to study drug, was non-serious. All abnormal laboratory changes were classified as mild or moderate, and no severe or very severe abnormal laboratory changes were observed.

Adverse events of interest

Infections and infestations

Infections and infestations were observed in 168/217 (77.4%) patients (Table 2). The most common infections were nasopharyngitis (123/217; 56.7%), pharyngitis (28/217; 12.9%), and gastroenteritis (22/217; 10.1%). Infections were classified as mild or moderate, with the exception of cellulitis and pneumonia (two patients each; 0.9%), bronchitis, subcutaneous abscess, acute sinusitis, appendicitis, osteomyelitis, bacterial arthritis, and pharyngeal abscess (one patient each, 0.5%), which were classified as severe, and one incidence of sepsis (0.5%), which was classified as very severe.

Serious infections were reported in 16/217 (7.4%) patients (Table 2). All of these serious infections were classified as related to study drug, and treatment was discontinued in two patients with osteomyelitis and sepsis/pharyngeal. However, many of the serious infections either resolved or were relieved with treatment. Opportunistic infections were observed in 33/217 (15.2%) treated patients; they included herpes zoster and oral herpes (ten patients each; 4.6%) and herpes simplex (3/217; 1.4%). Incidences of other opportunistic infections were less than 1.0%. No cases of tuberculosis were reported.

Neoplasms

Neoplasms—benign, malignant, and unspecified (including cysts and polyps)—were reported in 24/217 (11.1%) patients (Table 2). Of these, B-cell lymphoma, breast cancer, diffuse large B-cell lymphoma, endometrial cancer, gastric cancer, pancreatic carcinoma, pinealoma, T-cell lymphoma, lung neoplasm, and cervix carcinoma stage 0 (one patient each, 0.5%) were classified as malignant. Serious neoplasms occurred in 11/217 (5.1%) patients and included the above neoplasms that were classified as malignant (excluding lung neoplasm), an unspecified neoplasm, and uterine leiomyoma. Each of the neoplasms classified as both malignant and serious was classified as related to study drug, and the treatment with abatacept was discontinued.

Autoimmune events

Autoimmune AEs occurred in 8/217 (3.7%) patients (Table 2). Autoimmune events included scleritis, uveitis, atrophic gastritis, Sjögren's syndrome, erythema nodosum, leukocytoclastic vasculitis, Basedow's disease, and inflammatory bowel disease (IBD, one patient each; 0.5%). Only one autoimmune event (IBD) led to discontinuation; this event occurred in a new patient with MTX intolerance, was classified as serious, and was classified as related to study drug by the investigator.

Peri-infusional AEs

Peri-infusional AEs, defined as AEs that occurred after the start of treatment on the day of abatacept administration or the following day, occurred in 103/217 (47.5%) patients (Table 2). All events were classified as mild or moderate with the exception of one T-cell lymphoma and one cervix carcinoma stage 0 that were classified as severe.

Immunogenicity and pharmacodynamics

Immunogenicity

Immunogenicity was evaluated as auto-antibody productive responses in 217 patients using ELISA. Anti-abatacept antibody (23/217; 10.6%) or anti-CTLA-4-T antibody (20/217; 9.2%) were detected from Weeks 0 to 192 in a total of 42/217 (19.4%) patients. Patients with a positive anti-abatacept antibody response (23/217) were found in each of the three cohorts: Phase I, 2/13 (15.4%); Phase II, 19/178 (10.7%); and new patients with MTX intolerance, 2/26 (7.7%). Patients with a positive anti-CTLA-4-T antibody response (20/217; 9.2%) were detected in two of the three cohorts: Phase I, 0; Phase II, 19/178 (10.7%); and newly enrolled patients, 1/26 (3.8%). Among the patients from Phase II with positive immunogenicity responses, 20 were already anti-abatacept antibody (4/178; 2.2%) or anti-CTLA-4-T antibody (17/178; 9.6%) positive at baseline (Week 0) of this Phase III study. Of these patients, 17/178 (9.6%) did not test positive again during the Phase III study (post-baseline). Neutralizing activity was indicated in five patients from Phase II who tested positive for anti-CTLA-4-T antibody at baseline. However, no patients tested positive for neutralizing activity of anti-CTLA-4-T antibody during this Phase III study (post-baseline).

Pharmacodynamics

Pharmacodynamic parameters, including CRP and RF evaluations, improved with abatacept treatment. Mean CRP levels at baseline in Phase I, Phase II, and new patients with MTX intolerance were 1.84, 2.32, and 4.67 mg/dL, respectively (Table 1). In patients from Phase I and Phase II, CRP levels decreased to below the lower limit of the reference range (1 mg/dL) at Week 24, and remained so for over 3 years in the patients from Phase II. Similarly, in new patients with MTX intolerance, mean (SD) CRP level decreased to 0.9 (1.3) mg/dL at Week 48 ($n = 18$, baseline: 4.1 mg/dL) and remained consistently low for over 3 years. RF positivity decreased over time in each cohort. The overall mean RF value decreased from 255.0 IU/mL to 183.5 IU/mL at Week 24 ($n = 210$). The mean (standard error, SE) change from baseline was − 71.6 (13.7) IU/mL at Week 24, − 85.8 (17.4) IU/mL at Week 48, − 89.2 (22.3) IU/mL at Week 96, − 68.2 (23.9) IU/mL at Week 144, and − 176.2 (250.5) IU/mL at Week 192.

Clinical efficacy

ACR responses

Of the 217 patients treated with abatacept, 212 (97.7%) patients completed the efficacy evaluation at 6 months (24 weeks), 201 (92.6%) patients at 1 year (Week 48), 190 (87.6%) patients at 2 years (Week 96), and 167 (77.0%) patients at 3 years (Week 144: Figure 1). Only 11 (5.1%) patients had reached 4 years of treatment (Week 192) at the time of analysis, due to differential enrollment times. Therefore, it was considered possible to accurately evaluate the maintenance of efficacy of long-term administration of abatacept for up to 3 years (rates at 4 years are also given despite the very small sample size). Improvements in signs and symptoms of RA, as measured by ACR responses, were seen in high proportions of patients at Weeks 24 and 48, with ACR response rates maintained for patients who remained on abatacept therapy (as observed from baseline of the present study) for up to 3 years. The as-observed proportion of patients (95% confidence interval [CI]) from all cohorts achieving an ACR20 response at Weeks 24, 48, 96, 144, and 192 was 62.7% (55.8, 69.3), 65.7% (58.7, 72.2), 65.8% (58.6, 72.5), 70.1% (62.5, 76.9), and 81.8% (48.2, 97.7), respectively. For ACR50, as-observed response rates at Weeks 24, 48, 96, 144, and 192 were 28.3% (22.3, 34.9), 40.3% (33.5, 47.4), 38.9% (32.0, 46.3), 47.3% (39.5, 55.2), and 72.7% (39.0, 94.0), respectively. The as-observed proportion of patients with ACR70 response at Weeks 24, 48, 96, 144, and 192 was 11.8% (7.8, 16.9), 16.4% (11.6, 22.3), 18.9% (13.6, 25.3), 20.4% (14.5, 27.3), and 18.2 (2.3, 51.8), respectively. In a *post hoc* analysis, ACR responses were also evaluated using LOCF from baseline of the present study (Table 3) and were similar to the as-observed rates reported above.

ACR response (as-observed) was also analyzed for patients from the Phase II study based on baseline of Week 0 in the original Phase II study. During the Phase II study, ACR20, ACR50, and ACR70 response rates increased over time in the abatacept 10 mg/kg and abatacept 2 mg/kg groups [12]. By Week 24 of the Phase II study, the as-observed proportion of patients (95% CI) with ACR20, ACR50, and ACR70 response were, respectively: 78.3% (65.8, 87.9), 46.7% (33.7, 60.0), and 21.7% (12.1, 34.2) in the abatacept 10 mg/kg group ($n = 60$); 63.6% (50.9, 75.1), 37.9% (26.2, 50.7), and 16.7% (8.6, 27.9) in the abatacept 2 mg/kg group ($n = 66$); and 21.1% (11.4, 33.9), 5.3% (1.1, 14.6), and 0% (0.0, 6.3) in the placebo group ($n = 57$) [12]. The median transition period from the day of the final dose of the study drug in Phase II (Week 20) to the day of the first dose of abatacept in the present Phase III study was approximately 12 weeks for all dose groups. Following this transition and the switch to abatacept approximating 10 mg/kg for all patients, the respective as-observed ACR20, ACR50, and ACR70 response rates (based on Phase II baseline) at Week 24 of Phase III for the original Phase II dose groups were 81.4% (69.1, 90.3), 55.9% (42.4, 68.8), and 33.9% (22.1, 47.4) in the abatacept 10 mg/kg group ($n = 59$); 81.0% (69.1, 89.8), 50.8% (37.9, 63.6), and 25.4% (15.3, 37.9) in the abatacept 2 mg/kg group ($n = 63$); and 77.8% (64.4, 88.0), 50.0% (36.1, 63.9), and 29.6% (18.0, 43.6) in the placebo group ($n = 54$), respectively. At 3 years (Week 144 of Phase III), the respective as-observed ACR20, ACR50, and ACR70 response rates (based on Phase II baseline) for the original Phase II dose groups were 80.9% (66.7, 90.9), 61.7% (46.4, 75.5), and 40.4% (26.4, 55.7) in the abatacept 10 mg/kg group ($n = 47$); 87.2% (74.3, 95.2), 66.0% (50.7, 79.1), and 34.0% (20.9, 49.3) in the abatacept 2 mg/kg group ($n = 47$); and 91.7% (80.0, 97.7), 68.8% (53.7, 81.3), and 45.8% (31.4, 60.8) in the placebo group ($n = 48$), respectively.

Disease activity, physical function, and quality of life

Mean DAS28 (CRP) at baseline in patients from Phase I, Phase II, and in new patients with MTX intolerance was 4.4, 4.8, and 6.3, respectively. High proportions of patients achieved low disease activity (DAS28 [CRP] ≤ 3.2) and remission (DAS28 [CRP] < 2.6) outcomes at Weeks 24 and 48, and maintained these outcomes over time (based on as-observed data): 52.4 and 34.3%, respectively, at Week 24 ($n = 210$); 60.8 and 42.2%, respectively, at Week 48 ($n = 199$); 59.8 and 43.9%, respectively, at Week 96 ($n = 189$); 64.7 and 46.7%, respectively, at Week 144 ($n = 167$); and 54.5 and 45.5%, respectively, at Week 192 ($n = 11$). Additionally, DAS28 (CRP) analyzed using LOCF (Table 4) yielded rates similar to the as-observed analysis reported above; low disease activity and remission rates seen at Weeks 24 and 48 were sustained over the Phase III treatment period (Table 4).

Baseline HAQ scores are shown in Table 1. The as-observed proportion of patients (95% CI) achieving a HAQ response (defined as reduction of HAQ of > 0.3 from baseline) overall was 40.6% (33.9,

Table 3. ACR20, ACR50, and ACR70 responses at Weeks 24, 48, 96, 144, and 192 (LOCF from Phase III baseline).

	ACR responses			
	Patients from Phase I (IM101034), $n = 13$	Patients from Phase II (IM101071), $n = 178$	New patients with MTX intolerance, $n = 26$	Total (all treated patients), $N = 217$
Week 24				
ACR20, *n* (%)	10 (76.9)	106 (59.6)	18 (69.2)	134 (61.8)
95% CI for %	(46.2, 95.0)	(52.0, 66.8)	(48.2, 85.7)	(54.9, 68.2)
ACR50, *n* (%)	4 (30.8)	45 (25.3)	11 (42.3)	60 (27.6)
95% CI for %	(9.1, 61.4)	(19.1, 32.3)	(23.4, 63.1)	(21.8, 34.1)
ACR70, *n* (%)	1 (7.7)	19 (10.7)	5 (19.2)	25 (11.5)
95% CI for %	(0.2, 36.0)	(6.6, 16.2)	(6.6, 39.4)	(7.6, 16.5)
Week 48				
ACR20, *n* (%)	8 (61.5)	111 (62.4)	17 (65.4)	136 (62.7)
95% CI for %	(31.6, 86.1)	(54.8, 69.5)	(44.3, 82.8)	(55.9, 69.1)
ACR50, *n* (%)	2 (15.4)	66 (37.1)	14 (53.8)	82 (37.8)
95% CI for %	(1.9, 45.4)	(30.0, 44.6)	(33.4, 73.4)	(31.3, 44.6)
ACR70, *n* (%)	2 (15.4)	26 (14.6)	5 (19.2)	33 (15.2)
95% CI for %	(1.9, 45.4)	(9.8, 20.7)	(6.6, 39.4)	(10.7, 20.7)
Week 96				
ACR20, *n* (%)	9 (69.2)	108 (60.7)	16 (61.5)	133 (61.3)
95% CI for %	(38.6, 90.9)	(53.1, 67.9)	(40.6, 79.8)	(54.5, 67.8)
ACR50, *n* (%)	3 (23.1)	61 (34.3)	12 (46.2)	76 (35.0)
95% CI for %	(5.0, 53.8)	(27.3, 41.7)	(26.6, 66.6)	(28.7, 41.8)
ACR70, *n* (%)	1 (7.7)	31 (17.4)	4 (15.4)	36 (16.6)
95% CI for %	(0.2, 36.0)	(12.2, 23.8)	(4.4, 34.9)	(11.9, 22.2)
Week 144				
ACR20, *n* (%)	8 (61.5)	114 (64.0)	16 (61.5)	138 (63.6)
95% CI for %	(31.6, 86.1)	(56.5, 71.1)	(40.6, 79.8)	(56.8, 70.0)
ACR50, *n* (%)	4 (30.8)	74 (41.6)	12 (46.2)	90 (41.5)
95% CI for %	(9.1, 61.4)	(34.2, 49.2)	(26.6, 66.6)	(34.8, 48.3)
ACR70, *n* (%)	0 (0.0)	35 (19.7)	4 (15.4)	39 (18.0)
95% CI for %	(0.0, 24.7)	(14.1, 26.3)	(4.4, 34.9)	(13.1, 23.7)
Week 192				
ACR20, *n* (%)	9 (69.2)	111 (62.4)	17 (65.4)	137 (63.1)
95% CI for %	(38.6, 90.9)	(54.8, 69.5)	(44.3, 82.8)	(56.3, 69.6)
ACR50, *n* (%)	5 (38.5)	78 (43.8)	13 (50.0)	96 (44.2)
95% CI for %	(13.9, 68.4)	(36.4, 51.4)	(29.9, 70.1)	(37.5, 51.1)
ACR70, *n* (%)	0 (0.0)	40 (22.5)	6 (23.1)	46 (21.2)
95% CI for %	(0.0, 24.7)	(16.6, 29.3)	(9.0, 43.6)	(16.0, 27.2)

ACR, American College of Rheumatology; CI, confidence interval; LOCF, last observation carried forward; MTX, methotrexate

Table 4. DAS28 (CRP) LDAS and remission at Weeks 24, 48, 96, 144, and 192 (LOCF from Phase III baseline).

	LDAS and remission[a]			
	Patients from Phase I (IM101034), $n = 13$	Patients from Phase II (IM101071), $n = 178$	New patients with MTX intolerance, $n = 26$	Total (all treated patients), $N = 217$
Week 24				
LDAS, *n* (%)	9 (69.2)	95 (53.4)	6 (23.1)	110 (50.7)
Remission, *n* (%)	6 (46.2)	60 (33.7)	6 (23.1)	72 (33.2)
Week 48				
LDAS, *n* (%)	9 (69.2)	108 (60.7)	8 (30.8)	125 (57.6)
Remission, *n* (%)	4 (30.8)	78 (43.8)	5 (19.2)	87 (40.1)
Week 96[b]				
LDAS, *n* (%)	6 (46.2)	106 (59.9)	7 (26.9)	119 (55.1)
Remission, *n* (%)	3 (23.1)	79 (44.6)	5 (19.2)	87 (40.3)
Week 144				
LDAS, *n* (%)	6 (46.2)	113 (63.5)	9 (34.6)	128 (59.0)
Remission, *n* (%)	4 (30.8)	83 (46.6)	4 (15.4)	91 (41.9)
Week 192				
LDAS, *n* (%)	7 (53.8)	111 (62.4)	10 (38.5)	128 (59.0)
Remission, *n* (%)	4 (30.8)	86 (48.3)	7 (26.9)	97 (44.7)

DAS28 (CRP), 28-joint Disease Activity Score (C-reactive protein); LDAS, low disease activity state; LOCF, last observation carried forward; MTX, methotrexate.

[a]LDAS was defined as a DAS28 (CRP) of ≤ 3.2, and remission was defined as DAS28 (CRP) of < 2.6.

[b]At Week 96, 177 patients from Phase II were evaluated (Total = 216).

47.5) at Week 24 ($n = 212$), 43.8% (36.8, 50.9) at Week 48 ($n = 201$), 50.0% (42.7, 57.3) at Week 96 ($n = 190$), 50.3% (42.5, 58.1) at Week 144 ($n = 167$), and 90.9% (58.7, 99.8) at Week 192 ($n = 11$). As with the as-observed data reported above, initial improvement and subsequent maintenance of response over time also occurred when HAQ response was evaluated using LOCF (Table 5).

All cohorts showed an improvement from baseline in physical component summary and mental component summary scores of the SF-36 over 3 years. The mean (SE) change from baseline in physical component summary score for all cohorts combined was 8.4 (0.8) at Week 24, 10.2 (0.9) at Week 48, 10.7 (0.9) at Week 96, 8.6 (1.0) at Week 144, and 13.8 (6.3) at Week 192. The mean (SE) change from baseline in mental component summary score for all cohorts was 3.2 (0.6) at Week 24, 3.6 (0.6) at Week 48, 3.0 (0.7) at Week 96, 3.2 (0.7) at Week 144, and 11.5 (5.2) at Week 192. Improvement from baseline was also achieved in the eight SF-36 subscales (not shown).

Discussion

Although the majority of patients with RA begin long-term treatment with MTX, some patients do not respond adequately to MTX alone or are not candidates for MTX, and therefore require additional therapeutic options. Previous studies have demonstrated the long-term efficacy and favorable safety of IV abatacept in patients with an inadequate response to MTX [9,10]. In this long-term study in Japanese patients with RA and an inadequate response to MTX or other conventional or biologic DMARDs, IV abatacept monotherapy and IV abatacept with background MTX demonstrated acceptable safety and sustained efficacy over 3 years of treatment.

This Phase III, open-label, long-term study of IV abatacept included patients with RA from the Japanese Phase I clinical trial [13], patients with active RA and an inadequate response to MTX from the Japanese Phase II clinical trial [12], and newly enrolled patients with RA and MTX intolerance. Although all patients had

Table 5. Patients who presented HAQ response at Weeks 24, 48, 96, 144, and 192 (LOCF from Phase III baseline).

	HAQ response[a]			
	Patients from Phase I (IM101034), $n = 13$	Patients from Phase II (IM101071), $n = 178$	New patients with MTX Intolerance, $n = 26$	Total (all treated patients), $N = 217$
Week 24				
n (%)	5 (38.5)	70 (39.3)	12 (46.2)	87 (40.1)
95% CI for %	(13.9, 68.4)	(32.1, 46.9)	(26.6, 66.6)	(33.5, 46.9)
Week 48				
n (%)	4 (30.8)	73 (41.0)	15 (57.7)	92 (42.5)
95% CI for %	(9.1, 61.4)	(33.7, 48.6)	(36.9, 76.6)	(35.7, 49.3)
Week 96				
n (%)	6 (46.2)	81 (45.5)	15 (57.7)	102 (47.0)
95% CI for %	(19.2, 74.9)	(38.0, 53.1)	(36.9, 76.6)	(40.2, 53.9)
Week 144				
n (%)	7 (53.8)	82 (46.1)	13 (50.0)	102 (47.0)
95% CI for %	(25.1, 80.8)	(38.6, 53.7)	(29.9, 70.1)	(40.2, 53.9)
Week 192				
n (%)	8 (61.5)	80 (44.9)	14 (53.8)	102 (47.0)
95% CI for %	(31.6, 86.1)	(37.5, 52.6)	(33.4, 73.4)	(40.2, 53.9)

CI, confidence interval; HAQ, Health Assessment Questionnaire; LOCF, last observation carried forward; MTX, methotrexate

[a]HAQ response was defined as at least a 0.3-point decrease in HAQ score.

been treated previously with MTX, approximately one-third of patients also had prior biologic DMARD use. At enrollment, the majority of patients from the Phase I and Phase II studies were receiving concomitant MTX, and the newly enrolled patients received abatacept monotherapy. All patients were treated with IV abatacept for a mean of 3 years, and 58.1% patients were maintained on IV abatacept for more than 3 years.

The variety, frequency, and severity of the AEs in patients treated with abatacept as monotherapy or concomitantly with DMARDs were not significantly different from those reported in long-term international clinical trials of abatacept (NCT00162266 [19]; NCT00048568 [9]; and NCT00048581 [20]) and the Japanese Phase II clinical trial (NCT00345748 [12]). Most of the AEs observed, including abnormal laboratory changes, were mild or moderate, and most SAEs resolved or were relieved by treatment. Among the three patient cohorts, newly enrolled patients had the highest rates of SAEs and discontinuation due to SAEs. As expected, these patients also had higher baseline disease activity.

In addition to assessment of AEs, the immunogenicity results from the present study fall within the range of results seen in the previous Japanese trials [12,13]. During the Phase I study, 7/21 (33%) patients were positive for anti-CTLA-4-T antibodies [13], while positive immunogenicity responses were not detected in any patient during the Phase II study [12]. In the present study, the majority of patients with a positive immunogenicity response were from the Phase II study. Of these Phase II patients, approximately half had positive responses that were transient and occurred only at baseline.

Improvements from baseline in CRF and RF levels were demonstrated in all cohorts. Reductions in CRP have been shown to be correlated with clinical response in previous studies of abatacept [21,22]. The CRP reduction in the present study is also consistent with the Phase I Japanese trial that demonstrated mean decreases in CRP levels [13]. In a Phase II study of IV abatacept (~10 mg/kg) in patients with very early RA (NCT00124449), reductions in RF levels from baseline were seen at 6 months and 1 year, and, similar to CRP, changes in RF levels were correlated with clinical response to abatacept [23].

As this study was an uncontrolled, open-label study, and the evaluation of efficacy was a secondary objective, no tests based on a formal statistical hypothesis were conducted, and the efficacy was based on as-observed analyses for up to 3 years following baseline (Week 0) of this Phase III study. The majority of the 217 evaluated patients had previously received abatacept either as part of the Phase I study (2, 8, and 16 mg/kg abatacept) or as part of the Phase II trial (2 or 10 mg/kg abatacept or placebo plus MTX), and as such had lower mean clinical disease severity at baseline than the newly enrolled patients. Improvements in clinical efficacy were seen in patients from Phase I and Phase II following initiation of abatacept at Week 0, likely due to the transition period between studies, and the fact that not all patients had been receiving abatacept at therapeutic doses. Patients who were newly enrolled on abatacept as monotherapy experienced improvements in signs and symptoms of RA, as evaluated by ACR response, following initiation of therapy. Following the initial clinical response, ACR response rates were maintained over 3 years in all three patient cohorts.

For patients from Phase II, ACR response rates declined in both abatacept-treated groups (2 and 10 mg/kg) during the period between the last efficacy analysis of the Phase II study and the start of Phase III (data not shown). However, the ACR response rates increased in all treatment groups after the start of abatacept administration in Phase III. Based on baseline of Week 0 in the original Phase II study, ACR responses at Week 24 of this Phase III study for each of the original Phase II dose groups were similar to those observed for the abatacept 10 mg/kg group at Week 24 of the Phase II study [12]. Furthermore, based on a baseline of Week 0 in the original Phase II study, these response rates were sustained for up to 3 years in the present study for patients who remained on treatment.

DAS28 (CRP) and HAQ outcomes (based on as-observed data) were also maintained over the 3-year period in all patient cohorts, which included patients receiving IV abatacept as monotherapy and when administered with concomitant DMARDs, demonstrating sustained benefits in disease activity and physical function for patients who remained on treatment. Since as-observed analyses are vulnerable to the discontinuation of patients, a *post hoc* analysis using the more stringent LOCF method was performed for the above clinical efficacy measures. Using LOCF, rates of ACR response, DAS28 (CRP)-defined LDAS and remission, and HAQ response were sustained over 3 years, confirming the results from the as-observed analyses. Finally, SF-36 physical component summary and mental component summary scores (as-observed) also showed improvement from baseline in all cohorts, and generally continued at the same improved levels over the same time frame.

Interpretation of results should take into consideration the limitations of the study. This study, being an open-label extension, creates a number of challenges for data analysis and interpretation. These challenges, which include bias in patient inclusion and outcomes, have been previously outlined by Buch et al. [24]. Furthermore, the three cohorts utilized in this study had different baseline disease states with varying prior and current concomitant medication usage, and the results from the pooled patient population should be interpreted with caution. In addition, the sample size of this study was small; for this reason, the findings of this study alone should be extrapolated to the broader community with appropriate caution.

In conclusion, no new safety signals were identified in this long-term study of IV abatacept in Japanese patients with RA compared with previous international trials, based on the assessment of AEs and immunogenicity. IV abatacept as monotherapy and in combination with MTX was confirmed to be well tolerated, and improvements in clinical and functional efficacy were maintained for up to 3 years with continued treatment.

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Conflict of interest

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Supplementary material available online

Supplementary Tables 1 and 2.