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A Phase IIb Study of ABT-494, a Selective JAK-1 Inhibitor, in Patients With Rheumatoid Arthritis and an Inadequate Response to Anti–Tumor Necrosis Factor Therapy

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Objective. **To compare the efficacy and safety of ABT-494, a novel selective JAK-1 inhibitor, with placebo in patients with moderate-to-severe rheumatoid arthritis (RA) and an inadequate response or intolerance to at least 1 anti–tumor necrosis factor (anti-TNF) agent.**

Methods. **In this 12-week, double-blind, placebo-controlled, dose-ranging study, 276 RA patients receiving a stable dose of methotrexate (MTX) who had previously received treatment with at least 1 anti-TNF agent were randomized equally to receive immediate-release ABT-494 at 3, 6, 12, or 18 mg twice daily or matching placebo twice daily. The primary end point was the proportion of patients meeting the American College of Rheumatology 20% improvement criteria (achieving an ACR20 response) at week 12.**

Results. **At week 12, significantly more patients receiving ABT-494 (53–71%) than those receiving placebo (34%) achieved an ACR20 response (by nonresponder imputation analysis) ($P < 0.05$), with a dose-response relationship among all ABT-494 doses ($P < 0.001$). ACR50 and ACR70 response rates were significantly higher in those receiving ABT-494 (36–42% and 22–26%, respectively) than in those receiving placebo (16% and 4%, respectively). Changes from baseline in the Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) were significantly greater for all doses of ABT-494 than for placebo ($P \leq 0.01$). Onset of action of ABT-494 was rapid, with significant differences from placebo at week 2 both in ACR20 response rate (for 12 and 18 mg) and in change in the DAS28-CRP ($P < 0.001$ for 6–18 mg). The most frequent adverse events (AEs) were headache, nausea, upper respiratory tract infection, and urinary tract infection. Infection rates were higher at higher doses of ABT-494, but no infections were serious. No deaths were reported among those receiving ABT-494.**

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Conclusion. **In patients with an inadequate response or intolerance to anti-TNF agents, ABT-494 added to MTX showed rapid, dose-dependent improvements in RA signs and symptoms, with safety and tolerability similar to those of other drugs of this class. No new AEs were identified.**

Biologic agents are highly effective therapies that have greatly improved the standard of care for patients with rheumatoid arthritis (RA). However, there remains a need for new treatments, as not all patients experience sufficient disease control, and some lose responses over time (1,2). The inflammatory response may be modulated by inhibition of the JAKs, which are involved in the signaling pathways for several proinflammatory cytokines (3). The JAK family is composed of 4 members: JAK-1, JAK-2, JAK-3, and Tyk-2. These cytoplasmic tyrosine kinases are associated with membrane cytokine receptors, such as common γ-chain receptors and the gp130 transmembrane proteins (4).

A small-molecule, nonselective JAK inhibitor, tofacitinib, has recently emerged in the RA treatment paradigm, showing efficacy in different spectra of RA patients: methotrexate (MTX)–naive patients, inadequate responders to MTX, and inadequate responders to anti–tumor necrosis factor (anti-TNF) agents (5–9). Baricitinib, a JAK-1/JAK-2 inhibitor, also showed promising results in an RA phase III program (10–12). However, there are some safety concerns with this class of JAK inhibitors, particularly involving infections (including herpes zoster), malignancies, and hematologic adverse events (AEs) (5,11–13).

ABT-494 is a selective JAK-1 inhibitor being developed for the treatment of adult patients with moderately to severely active RA. Interleukin-6 (IL-6) and the interferons (IFNs) are known to signal primarily through JAK-1, and based on the proven action of tocilizumab in RA, which functions via IL-6 inhibition, JAK-1 is thought to play an important role in RA disease pathophysiology. In biochemical assays, ABT-494 is ~74-fold more selective for JAK-1 than for JAK-2 (which is involved in erythropoiesis) and ~58-fold more selective for JAK-1 than for JAK-3 (which is involved in immunosurveillance) (14). The enhanced selectivity of ABT-494 for JAK-1 over JAK-2 and JAK-3 (13) may offer an improved benefit–risk profile in patients with RA. In phase I trials, ABT-494 was found to be safe and well-tolerated up to multiple doses of 24 mg twice daily using the immediate release formulation in healthy volunteers and in subjects with RA. ABT-494 exposure was dose proportional in the evaluated multiple dose range (3–24 mg twice daily) (15).

The safety and efficacy of ABT-494 were evaluated in 2 phase IIb, dose-ranging, randomized, placebo-controlled studies in patients with moderately to severely active RA. This report presents the results from 1 of these 2 studies, BALANCE I, which evaluated the safety and efficacy of 4 doses of ABT-494 compared with placebo in patients who had had intolerance to at least 1 anti-TNF therapy or for whom at least 1 anti-TNF therapy had failed.

PATIENTS AND METHODS

Patients. Adult men and women age ≥18 years diagnosed as having RA and fulfilling either the American College of Rheumatology (ACR) 1987 revised classification criteria (16) or the ACR/European League Against Rheumatism 2010 classification criteria (17) were enrolled in the study. Active RA was defined as having ≥6 swollen joints (based on a 66-joint count), ≥6 tender joints (based on a 68-joint count), and either a high-sensitivity C-reactive protein (hsCRP) level above the upper limit of normal (ULN) (5 mg/liter) or seropositivity for both rheumatoid factor and anti–cyclic citrullinated peptide. Eligible patients must have continued to have active RA despite being treated with at least 1 anti-TNF biologic agent for ≥3 months, or they must have discontinued anti-TNF biologic therapy because of intolerance or toxicity. In addition, patients with prior exposure to non–anti-TNF biologic therapy were allowed to enroll as long as at least 1 anti-TNF biologic agent had failed to be effective for treating their disease. All biologic agents had to be washed out prior to randomization (≥4 weeks for etanercept; ≥8 weeks for adalimumab, infliximab, certolizumab, and golimumab; >8 weeks for abatacept; >12 weeks for tocilizumab; and >1 year for rituximab). Patients must have been receiving a stable dose (7.5–25 mg/week) of MTX (oral or parenteral) for ≥4 weeks prior to study initiation. Key exclusion criteria were prior exposure to a JAK inhibitor or need for any immunosuppressive agent other than MTX. Subjects with serum aspartate transaminase (AST) levels or alanine transaminase (ALT) levels >1.5× ULN, absolute neutrophil counts <1,200/μl, or absolute lymphocyte counts <750/μl at screening were excluded.

Study design and treatment. BALANCE I was a phase IIb, 12-week, randomized, double-blind, parallel-group, placebo-controlled study conducted at 123 sites, enrolling patients in the US (176 patients, 64%), Puerto Rico (11 patients, 4%), Australia and New Zealand (6 patients, 2%), Western Europe including Belgium, Spain, and Great Britain (29 patients, 11%), and Eastern Europe including Czech Republic, Hungary, and Poland (54 patients, 20%). The study was initiated in October 2013 and was completed by the last patient in July 2015.

Patients were randomized equally to receive oral immediate-release doses of ABT-494 twice daily at 3 mg, 6 mg, 12 mg, or 18 mg, or matching placebo twice daily, for 12 weeks. Randomization was performed centrally, according to a blocked randomization schedule previously generated by the AbbVie statistics department, by investigators enrolling patients via an interactive voice response system. Patients, caregivers, investigators, joint assessors, and the AbbVie study team were blinded to the treatment administered. Placebo and

ABT-494 capsules were identical in appearance. Patients should have been taking an oral supplement of folic acid (or equivalent) from 4 weeks prior to baseline and throughout the study. Patients were required to continue stable doses of MTX and nonsteroidal antiinflammatory drugs, acetaminophen, or oral corticosteroids (equivalent to prednisone at ≤10 mg/day).

The study was conducted in accordance with the International Conference on Harmonisation guidelines, applicable regulations, and the principles of the Declaration of Helsinki. The study protocol was approved by an independent ethics committee or institutional review board. All patients provided written informed consent before participating in any study-related procedures.

Assessments. The primary efficacy end point was the proportion of patients meeting the ACR 20% improvement criteria (achieving an ACR20 response) (18) at week 12. Secondary end points included the proportions of patients achieving an ACR50/ACR70 response and the proportion of patients achieving a Disease Activity Score in 28 joints (19) using the CRP (DAS28-CRP) of ≤3.2 or <2.6 at week 12. Among the other end points were the proportion of patients achieving low disease activity or clinical remission based on Clinical Disease Activity Index (CDAI) (20) criteria (CDAI score ≤10 indicates low disease activity; CDAI score ≤2.8 indicates clinical remission), change in the DAS28-CRP, change in individual components of the ACR core set of disease activity measures (21), and the proportion of patients achieving a minimum clinically important difference (MCID) of −0.22 on the Health Assessment Questionnaire disability index (HAQ DI) (22–24). Changes in the Simplified Disease Activity Index (SDAI) (25) were calculated post hoc. A post hoc analysis was performed to determine the proportion of patients who had a sustained ACR20 response, defined as meeting the ACR 20% improvement criteria at every visit (at weeks 2, 4, 6, 8, and 12).

Laboratory analyses were conducted by a central laboratory. After study completion and database lock, the central laboratory informed AbbVie that one lot of the reagent used to detect hsCRP had expired early (Roche lot 604450) and resulted in underreporting by 3–13% (<0.1–0.4 mg/liter) of a subset of samples with levels below the ULN (16% of week 12 samples). Sensitivity analyses using a larger-than-expected correction factor (20% inflation) on the affected samples were performed (for ACR20/ACR50/ACR70 response rates, response rates for low disease activity and clinical remission according to the DAS28-CRP, and hsCRP level over time as a continuous variable).

Safety was evaluated at each scheduled visit during treatment and for 30 days after the last dose of study drug on the basis of AEs, serious AEs (SAEs), vital signs, and results of laboratory tests (hematology, blood chemistry, and urinalysis). Adverse events were coded according to the Medical Dictionary for Regulatory Activities (version 17.1). Descriptions of AE severity and postbaseline changes in laboratory test results were based on the Rheumatology Common Toxicity Criteria version 2.0, developed by the Outcome Measures in Rheumatology Drug Safety Working Group (26). An independent committee of experts adjudicated potential cardiovascular events in a blinded manner in accordance with the cardiovascular adjudication committee charter.

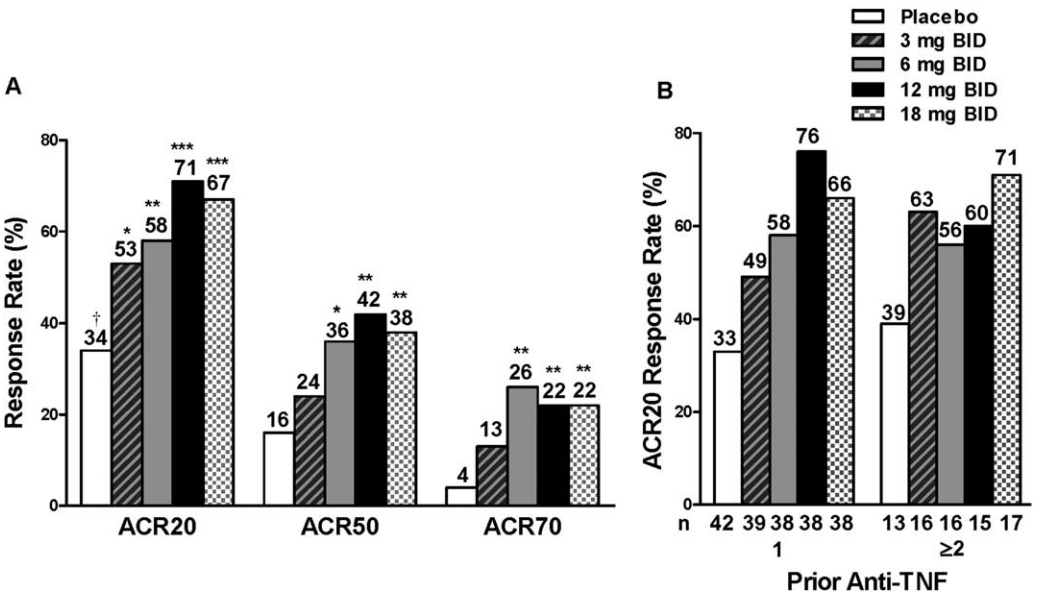

Figure 1. A, Percentages of patients with rheumatoid arthritis achieving a response to ABT-494 at 3, 6, 12, or 18 mg twice daily (BID) or to matching placebo twice daily according to the American College of Rheumatology criteria for 20% improvement (ACR20), 50% improvement, and 70% improvement at week 12 (nonresponder imputation [NRI] analysis). † = the sensitivity analyses for correction of affected high-sensitivity C-reactive protein samples predicted a potential shift of 1 subject from responder to nonresponder in the placebo arm for an ACR20 response (from 34% to 32%). * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$ versus placebo. **B,** ACR20 responses at week 12 by number of previously received anti–tumor necrosis factor (anti-TNF) agents (NRI analysis). *P* values were not calculated for ACR20 responses based on number of previously received anti-TNF agents. Results in both panels are shown for the modified intent-to-treat population.

Table 1. Baseline characteristics and disease activity of the patients in the modified intent-to-treat population*

	Placebo (n = 56)	ABT-494 3 mg twice daily (n = 55)	ABT-494 6 mg twice daily (n = 55)	ABT-494 12 mg twice daily (n = 55)	ABT-494 18 mg twice daily (n = 55)
Characteristic					
Women, no. (%)	48 (86)	43 (78)	43 (78)	45 (82)	42 (76)
Age, years	58 ± 12	57 ± 13	56 ± 12	59 ± 11	57 ± 12
Duration since RA diagnosis, years	12.1 ± 9.0	11.8 ± 9.4	12.3 ± 10.6	12.2 ± 10.2	10.9 ± 7.7
RF positive, no. (%)	49 (88)	43 (78)	45 (82)	45 (82)	48 (87)
Anti-CCP positive, no. (%)	48 (86)	45 (82)	45 (82)	45 (82)	47 (86)
Methotrexate dose, mg/week	19 ± 19	17 ± 5	17 ± 5	17 ± 5	19 ± 16
Previously received only 1 anti-TNF agent, no. (%)	42 (76)	39 (71)	38 (70)	38 (72)	38 (69)
Previously received ≥2 anti-TNF agents, no. (%)	13 (24)	16 (29)	16 (30)	15 (28)	17 (31)
Previously received non–anti-TNF biologic agents, no. (%)	9 (16)	10 (18)	14 (26)	14 (26)	7 (13)
Disease activity					
TJC of 68 joints	28 ± 15	28 ± 15	30 ± 16	26 ± 16	26 ± 15
TJC of 28 joints	16 ± 7	16 ± 7	17 ± 7	15 ± 7	15 ± 7
SJC of 66 joints	19 ± 12	17 ± 10	17 ± 10	17 ± 10	18 ± 10
SJC of 28 joints	13 ± 6	12 ± 6	12 ± 5	11 ± 6	14 ± 7
PtGA, 0–100-mm VAS	66 ± 21	64 ± 20	69 ± 21	71 ± 20	66 ± 20
Patient's assessment of pain, 0–100-mm VAS	67 ± 21	63 ± 18	71 ± 21	69 ± 18	68 ± 16
PhGA, 0–100-mm VAS	64 ± 15	67 ± 15	65 ± 15	67 ± 16	64 ± 16
HAQ DI score, range 0–3	1.6 ± 0.7	1.5 ± 0.7	1.6 ± 0.7	1.6 ± 0.6	1.5 ± 0.6
DAS28-CRP	5.8 ± 0.9	5.7 ± 0.9	5.9 ± 0.9	5.7 ± 0.9	5.8 ± 1.0
CDAI score	41 ± 12	40 ± 13	42 ± 12	40 ± 12	41 ± 14
hsCRP, mg/liter†	10.1 ± 13.2	11.4 ± 11.8	18.6 ± 27.4	14.4 ± 23.0	14.0 ± 15.1
hsCRP >ULN, no. (%)†‡	28 (50)	35 (64)	34 (62)	33 (60)	35 (64)

* Percentages were calculated using nonmissing values. Except where indicated otherwise, values are the mean ± SD. RA = rheumatoid arthritis; anti-TNF = anti–tumor necrosis factor; TJC = tender joint count; SJC = swollen joint count; PtGA = patient's global assessment of disease activity; VAS = visual analog scale; PhGA = physician's global assessment of disease activity; HAQ DI = Health Assessment Questionnaire disability index; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level; CDAI = Clinical Disease Activity Index.
† Patients with normal high-sensitivity CRP (hsCRP) levels could be enrolled as long as they were positive for rheumatoid factor (RF) and anti–cyclic citrullinated peptide (anti-CCP).
‡ Upper limit of normal (ULN) 5 mg/liter.

Statistical analysis. All efficacy analyses were conducted in the modified intent-to-treat population, which consisted of all randomized patients who received ≥1 dose of study drug. For ACR response rates, the last observation carried forward (LOCF) method was the primary missing data imputation method. Nonresponder imputation (NRI) was used to assess the robustness of the results and is also reported. For continuous end points including the DAS28-CRP, LOCF imputation of missing data was implemented; NRI is reported for binary end points. Binary end points including ACR response rates were analyzed using a chi-square test with normal approximation when comparing each ABT-494 treatment group to the placebo group. Continuous end points were analyzed using an analysis of covariance model with treatment group as a factor and baseline measurement as the covariate. The multiple comparison procedure and modeling method was implemented to detect any nonflat dose-response relationship by evaluating several nonlinear dose-response models at the same time. *P* values were not corrected for multiple comparisons. Assuming ACR20 response rates of 25% in the placebo group and 55% in any ABT-494 treatment group, a sample size of 50 patients per group (250 patients total) was estimated to provide at least 80% power to detect a 30% difference in response rates between the placebo group and an ABT-494 treatment group when using a 1-sided test with an alpha level of 0.05.

RESULTS

Patient disposition and baseline characteristics. A total of 276 patients were randomized; all received their intended treatment. The overall study completion rate was 88% (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39801/abstract). Baseline patient characteristics and disease activity were generally similar among treatment groups (Table 1). The mean ± SD disease duration since RA diagnosis was 11.9 ± 9.4 years. Seventy-two percent of patients had prior exposure to only 1 anti-TNF agent and 28% to at least 2 anti-TNF agents, and 20% of patients were exposed to non–anti-TNF biologic agents in addition to at least 1 anti-TNF agent. At baseline, patients had a mean ± SD of 17.6 ± 10.4 swollen joints (of 66 joints) and 27.6 ± 15.3 tender joints (of 68 joints); 60% of patients had an elevated hsCRP level, and the mean ± SD DAS28-CRP was 5.8 ± 0.9.

Efficacy. The primary analysis based on the LOCF method revealed that compared with 35% of

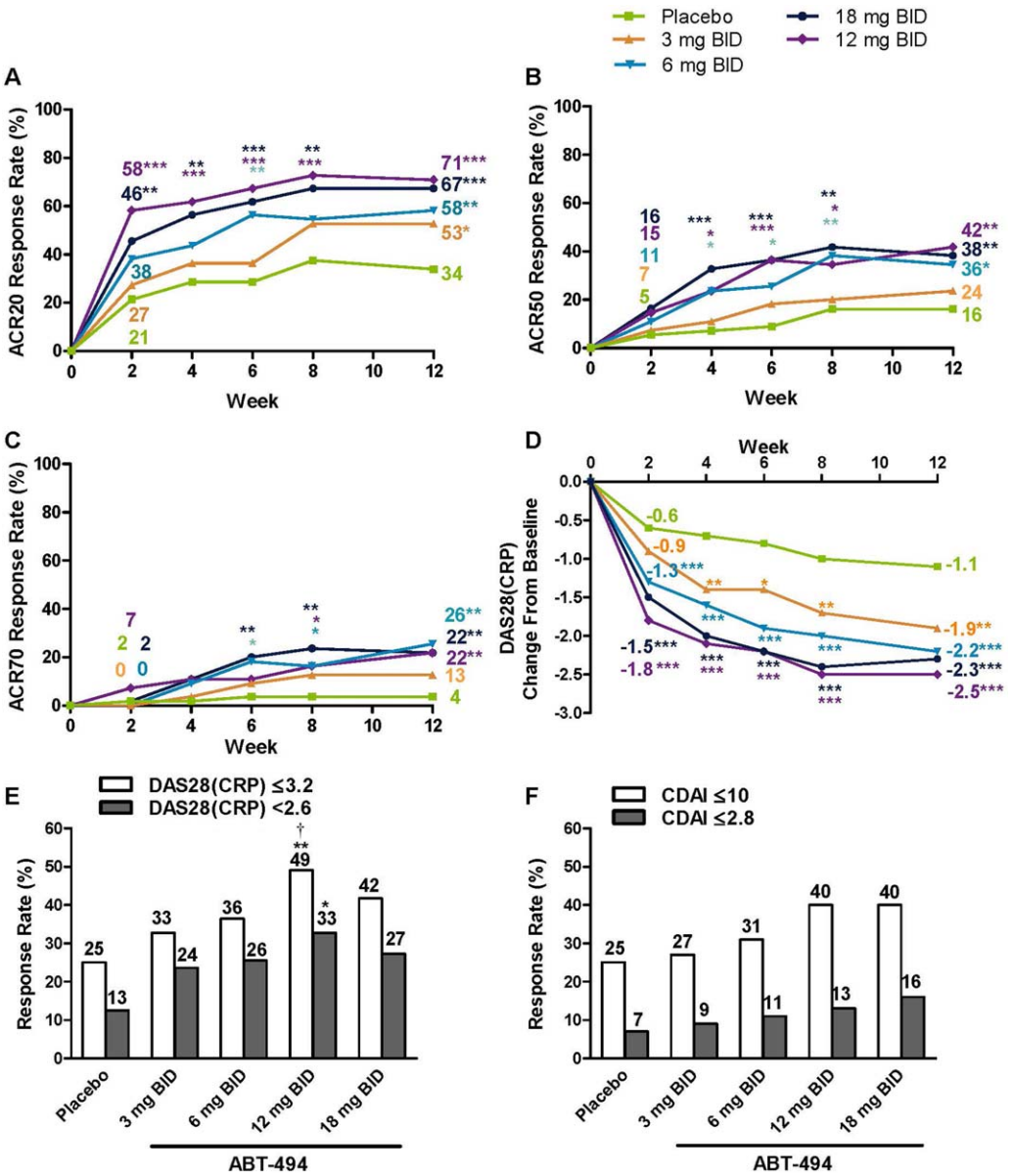

Figure 2. Responses of patients with rheumatoid arthritis to ABT-494 or placebo. **A,** ACR20 responses over time (NRI analysis). **B,** ACR50 responses over time (NRI analysis). **C,** ACR70 responses over time (NRI analysis). **D,** Mean change from baseline in Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) (last observation carried forward analysis). **E** and **F,** Patients achieving a DAS28-CRP of ≤3.2 or <2.6 (NRI analysis) (**E**) and low disease activity (score ≤10) or clinical remission (score ≤2.8) according to Clinical Disease Activity Index (CDAI) criteria (NRI analysis) (**F**) with ABT-494 treatment or placebo at week 12. Results in all panels are shown for the modified intent-to-treat population. † = the sensitivity analyses for correction of affected high-sensitivity CRP samples predicted a potential shift of 1 subject from responder to nonresponder in the 12 mg treatment arm for a DAS28-CRP of ≤3.2 (from 49% to 47%). * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$ versus placebo. See Figure 1 for other definitions.

patients who received placebo, an ACR20 response was achieved by 56% ($P = 0.033$), 64% ($P = 0.004$), 73% ($P < 0.001$), and 71% ($P < 0.001$) of patients treated with ABT-494 at 3, 6, 12, and 18 mg, respectively. Analysis based on NRI also demonstrated a statistically significant improvement in ACR20 response rate in patients who received any dose of ABT-494 (53% [$P = 0.046$], 58% [$P < 0.01$], 71% [$P < 0.001$], and 67% [$P < 0.001$] at 3, 6, 12, and 18 mg, respectively) compared with those who received placebo (34%) (Figure 1A). A significant dose-response relationship was observed for all doses of ABT-494 ($P < 0.001$). The

Table 2. Changes from baseline in disease activity measures of the American College of Rheumatology core set at week 12 in the modified intent-to-treat population using last observation carried forward analysis*

Disease activity measure	Placebo (n = 55)	ABT-494 3 mg twice daily (n = 54)	ABT-494 6 mg twice daily (n = 53)	ABT-494 12 mg twice daily (n = 55)	ABT-494 18 mg twice daily (n = 55)
TJC of 68 joints	−9.3 (−12.5, −6.1)	−13.4 (−16.6, −10.1)	−15.7 (−19.0, −12.5)†	−16.8 (−20.1, −13.6)†	−15.1 (−18.3, −11.9)‡
SJC of 66 joints	−6.4 (−8.7, −4.2)	−9.5 (−11.8, −7.3)	−9.2 (−11.5, −6.9)	−10.0 (−12.3, −7.8)‡	−9.2 (−11.5, −7.0)
Patient's assessment of pain, 0–100-mm VAS	−16.5 (−23.5, −9.5)	−24.7 (−31.8, −17.6)	−31.4 (−38.6, −24.2)†§	−36.3 (−43.3, −29.3)¶	−35.0 (−42.0, −27.9)§¶
PhGA, 0–100-mm VAS	−29.6 (−35.3, −23.8)#	−33.8 (−39.4, −28.1)	−37.5 (−43.2, −31.7)	−43.5 (−49.1, −37.9)¶	−42.4 (−48.0, −36.8)†
PtGA, 0–100-mm VAS	−20.0 (−27.0, −13.0)	−24.2 (−31.3, −17.1)	−29.9 (−37.1, −22.6)§	−37.4 (−44.4, −30.4)¶	−33.5 (−40.6, −26.5)†§
HAQ DI score, range 0–3	−0.2 (−0.4, −0.1)	−0.3 (−0.4, −0.1)	−0.5 (−0.6, −0.3)†§	−0.5 (−0.6, −0.3)‡	−0.5 (−0.7, −0.4)†§
HAQ DI score ≥MCID, no. (%)/ (95% CI)	24 (44)/(31, 57)	27 (50)/(37, 63)	30 (58)/(44, 71)	35 (64)/(51, 76)	34 (63)/(50, 76)
hsCRP, mg/liter	−0.4 (−4.6, 3.9)	−7.9 (−12.2, −3.6)‡	−9.7 (−14.1, −5.4)†	−6.8 (−11.1, −2.6)‡	−6.9 (−11.1, −2.6)‡

* Except where indicated otherwise, values are the mean (95% confidence interval [95% CI]); 95% CIs were calculated based on a normal approximation to the binomial distribution. MCID = minimum clinically important difference (−0.22 for HAQ DI score) (see Table 1 for other definitions).
† $P < 0.01$ versus placebo.
‡ $P < 0.05$ versus placebo.
§ Data were missing for 1 patient.
¶ $P < 0.001$ versus placebo.
# Data were missing for 2 patients.

Table 3. Summary of AEs*

	Placebo (n = 56)	ABT-494 3 mg twice daily (n = 55)	ABT-494 6 mg twice daily (n = 55)	ABT-494 12 mg twice daily (n = 55)	ABT-494 18 mg twice daily (n = 55)
Any AE	25 (45)	26 (47)	31 (56)	37 (67)	39 (71)
Any SAE	1 (2)	2 (4)	2 (4)	0	1 (2)
Any severe AE	2 (4)	1 (2)	2 (4)	2 (4)	1 (2)
Any AE leading to discontinuation	2 (4)	0	6 (11)	2 (4)	2 (4)
Any death	0	0	0	0	0
AEs of special interest†					
Infection	13 (23)	11 (20)	12 (22)	22 (40)	21 (38)
Serious infection	1 (2)	0	0	0	0
Herpes zoster	2 (4)	1 (2)	0	1 (2)	1 (2)
Opportunistic infection	0	0	0	1 (2)‡	0
Cardiovascular event	0	0	1 (2)§	0	0
Hepatic disorder	1 (2)	0	0	0	2 (4)
Malignancy	0	0	1 (2)¶	0	0

* Values are the number (%) of patients. AE = adverse event; SAE = serious AE.
† Reported by the investigator.
‡ Oral candidiasis.
§ Adjudicated as a transient ischemic attack by an externally led cardiovascular adjudication committee.
¶ Basal cell and squamous cell carcinoma.

ACR20 response rates at week 12 were similar for patients who had previously received 1 anti-TNF agent and those who had previously received at least 2 anti-TNF agents (by NRI analysis) (Figure 1B). In all patients, ACR50 and ACR70 response rates with ABT-494 doses of ≥6 mg were significantly higher than those with placebo (by NRI analysis) (Figure 1A).

Significant differences versus placebo in ACR20 response rates were observed at the first postbaseline assessment (week 2) in patients treated with ABT-494 at 12 and 18 mg (by NRI analysis) ($P \leq 0.007$) (Figure 2A); the maximum response rate (71%) was observed with the 12 mg dose by week 8 and plateaued thereafter. Starting at week 4, ACR50 response rates were significantly greater with ABT-494 at ≥6 mg than with placebo; the maximum response rate (42%) was observed with 18 mg by week 8 and plateaued thereafter (by NRI analysis) (Figure 2B). Higher ACR70 response rates versus placebo in the ABT-494 treatment groups were observed beginning at week 6, with a peak response of up to 26% at week 12 (by NRI analysis) (Figure 2C). A sustained ACR20 response (by NRI analysis; at every visit from week 2 to week 12) was achieved by 13%, 22%, 40%, and 27% of patients receiving ABT-494 at 3, 6, 12, and 18 mg, respectively, versus 4% of patients receiving placebo. Significant improvements versus placebo in the DAS28-CRP occurred at the week 2 assessment with ABT-494 at ≥6 mg (by LOCF method) ($P < 0.001$) (Figure 2D). Starting at week 4 and thereafter, significant improvements versus placebo in the DAS28-CRP were observed at all doses of ABT-494. Significant differences versus placebo in CDAI and SDAI scores were also observed from week 2 onward with ABT-494 at ≥6 mg (by LOCF method) (see Supplementary Figures 2A and F, http://onlinelibrary.wiley.com/doi/10.1002/art.39801/abstract). Changes in hsCRP levels over time are presented in Supplementary Figure 2C.

A higher percentage of patients receiving ABT-494 (any dose) than those receiving placebo achieved a DAS28-CRP of ≤3.2 or <2.6 at week 12 (by NRI analysis) (Figure 2E), with the difference being statistically significant at 12 mg (for a DAS28-CRP of ≤3.2, 49% versus 25% [$P < 0.01$]; for a DAS28-CRP of <2.6, 33% versus 13% [$P < 0.05$]). Similarly, a higher percentage of patients receiving ABT-494 (any dose) than those receiving placebo met the CDAI criteria for low disease activity or clinical remission at week 12 (by NRI analysis) (Figure 2F). At week 12, mean changes from baseline in each disease activity measure of the ACR core set were significantly greater with ABT-494 at 12 mg than with placebo (Table 2). In addition, a greater proportion of patients achieved the MCID for the HAQ DI score with ABT-494 at ≥6 mg (58–64%) than with placebo (44%). Sensitivity analyses for correction of affected hsCRP samples demonstrated the following: the population hsCRP value over time was predicted not to change; there was a potential shift of 1 subject from responder to nonresponder in the placebo arm for ACR20 response (from 34% to 32%) and for a DAS28-

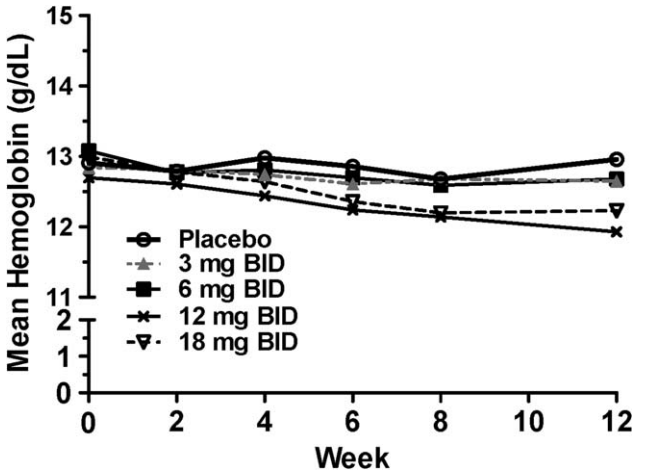

Figure 3. Mean hemoglobin levels over time in patients with rheumatoid arthritis receiving ABT-494 at 3, 6, 12, or 18 mg twice daily (BID) or matching placebo twice daily. Normal ranges for hemoglobin are 11.5–15.5 gm/dl in women and 13.2–17.0 gm/dl in men. Safety population with observed data.

CRP of ≤3.2 in the 12 mg ABT-494 arm (from 49% to 47%).

Safety. The percentage of patients with any treatment-emergent AE was numerically higher for ABT-494 than for placebo and increased in a dose-dependent manner with ABT-494 at 6, 12, and 18 mg (Table 3). However, the majority of reported AEs were considered mild to moderate in severity. The most commonly observed AEs were headache, nausea, upper respiratory tract infection, and urinary tract infection. The incidences of SAEs and severe AEs were low, without an apparent dose-response relationship (Table 3). Five patients treated with ABT-494 reported 7 SAEs (at 3 mg, 1 with pancreatitis and 1 with pulmonary embolism; at 6 mg, 1 with pulmonary embolism and deep vein thrombosis and 1 with transient ischemic attack [TIA] and benign prostate hyperplasia; at 18 mg, 1 with acute respiratory failure). One patient receiving placebo experienced an SAE of bronchiectasis.

The overall infection rates were similar for those treated with 3 mg ABT-494, 6 mg ABT-494, and placebo (20%, 22%, and 23%, respectively), but were higher for those treated with 12 mg and 18 mg ABT-494 (40% and 38%, respectively). No serious infections were reported in any of the ABT-494 treatment groups. Herpes zoster occurred in 2 patients in the placebo group (4%) and in 3 patients who received ABT-494 (1 patient [2%] each in the 3, 12, and 18 mg groups; each case was isolated to a single dermatome). Two reported events of hepatic disorders in the 18 mg group and 1 reported event in the placebo group were attributed to increased levels of transaminases or bilirubin; patients were asymptomatic, none of the events was serious, and none led to discontinuation from the study. The external cardiovascular adjudication committee adjudicated 1 case of TIA in 1 patient receiving 6 mg ABT-494 (reported as moderate by the investigator). One patient in the 6 mg group had 1 event each of basal cell carcinoma and squamous cell carcinoma. There was 1 case of opportunistic infection (oral candidiasis) in 1 patient receiving 12 mg ABT-494. No deaths were reported during the study period.

Elevations of serum transaminases (AST or ALT) were transient with no apparent dose relationship and did not result in early discontinuation from the study. Of the patients with normal ALT or AST levels at baseline, 12 of 208 (5.8%) receiving ABT-494 had elevated ALT levels (>1× ULN) at least twice, and 28 of 206 (13.6%) had elevated AST levels (>1× ULN) at least twice, compared with 2% and 6%, respectively, of patients receiving placebo. There were no cases of grade 4 AST or ALT abnormalities (see Supplementary Table 1, http://onlinelibrary.wiley.com/doi/10.1002/art.39801/abstract). Fifteen of 201 patients (7.5%) receiving ABT-494 who had normal creatinine levels at baseline experienced elevated creatinine levels (>1× ULN) at least twice, compared with none receiving placebo. A single case of grade 3 creatinine abnormality was observed in those receiving 18 mg ABT-494. Dose-dependent increases in low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol were observed (see Supplementary Figures 3C and D, http://onlinelibrary.wiley.com/doi/10.1002/art.39801/abstract); however, the ratios of LDL cholesterol to HDL cholesterol remained unchanged from baseline (see Supplementary Table 2, http://onlinelibrary.wiley.com/doi/10.1002/art.39801/abstract).

Decreases in mean hemoglobin levels from baseline were observed in a dose-dependent manner with ABT-494, although mean hemoglobin levels remained within the normal range across all dose groups during the study (Figure 3). Of the patients with normal hemoglobin levels at baseline, 23 of 219 (10.5%) who were treated with ABT-494 experienced decreased hemoglobin levels (grade 2 or above) at least twice, with the majority of those patients receiving 12 mg or 18 mg ABT-494. Eight of 219 patients (3.7%) had a maximum grade 4 decrease (reduction of ≥3.0 gm/dl) in hemoglobin level. One patient discontinued the study early due to a reported AE of low hemoglobin (reduction of 2.6 gm/dl). However, at the time of discontinuation, the hemoglobin level (13.2 gm/dl) was within the normal range (baseline level of 15.8 gm/dl).

Decreases in mean numbers of circulating lymphocytes and neutrophils were also observed (see Supplementary Table 1 and Supplementary Figure 3, http://onlinelibrary.wiley.com/doi/10.1002/art.39801/abstract), and 1 patient discontinued study drug due to leukopenia. Two patients receiving 18 mg ABT-494 had a grade 4 lymphocyte reduction (Supplementary Table 1); one was reported to have a vaginal yeast infection, and the other was reported to have herpes zoster around the time of lymphocyte reduction. One patient each in the 3 mg and 6 mg ABT-494 groups had a grade 4 lymphocyte reduction; however, the lymphocyte reductions did not coincide with infections. One patient receiving 12 mg ABT-494 had a grade 4 neutrophil reduction; no infections were reported at the time of neutropenia.

Reductions in natural killer (NK) cells (CD3−CD16+CD56+) appeared to be dose-related (see Supplementary Figure 4 and Supplementary Methods, http://onlinelibrary.wiley.com/doi/10.1002/art.39801/abstract). The mean ± SD change in NK cells was 16.5 ± 46.6% in the placebo group; a dose-dependent decrease was seen in patients treated with ABT-494 (−15.8 ± 25.3%, −18.3 ± 47.4%, −28.0 ± 37.3%, and −42.6 ± 31.7% at 3, 6, 12, and 18 mg, respectively; $P < 0.001$ for all comparisons).

DISCUSSION

Although the use of biologic agents for the treatment of RA is widespread and established, there is an unmet medical need for those patients who do not respond adequately or have intolerance to currently available biologic disease-modifying antirheumatic drugs. To date, several JAK inhibitors (6–8,10–12) have demonstrated significant clinical improvement in RA, firmly establishing that cytokines such as IL-6 and the IFNs, which signal through the JAK pathway, are important contributors to the pathology of RA. ABT-494 is a novel JAK-1 inhibitor designed to inhibit JAK-1 with greater selectivity compared with JAK-2 and JAK-3. In this study, we tested a broad dose range (up to 18 mg twice daily) of immediate-release ABT-494 to determine the dose(s) providing an optimal balance of safety and efficacy in patients with an inadequate response or intolerance to anti-TNF biologic therapies.

This is the first phase II study with any JAK inhibitor in patients for whom anti-TNF therapy has failed. At all doses, ABT-494 demonstrated rapid and robust efficacy, as shown by significantly greater improvements in clinical and functional outcomes compared with placebo. The onset of improvement was noted as early as 2 weeks after ABT-494 treatment (first postbaseline assessment), with up to 58% of patients achieving an ACR20 response. In addition, the peak ACR20, ACR50, and ACR70 response rates were observed before week 12. This is in contrast to the 3–6 months needed for many biologic therapies to achieve maximum efficacy (27–29), and comparable with observations for other JAK inhibitors, such as baricitinib and tofacitinib, in patients with an inadequate response to anti-TNF agents (6,11). Although the sample size was small, the ACR20 response rate was comparable between patients who had previously received ≥2 anti-TNF agents and those who had previously received only 1 anti-TNF agent. The underreporting of a minority of hsCRP values was predicted to have no significant impact on efficacy parameters and the overall conclusions for the study.

Although they produce significant clinical improvement in different spectra of RA patients, there are safety concerns with JAK inhibitors; these predominantly involve impairment of the body's ability to fight infections, viral reactivation, and alteration of hematopoietic homeostasis, the last of which could be associated with anemia. Increases in total cholesterol, elevation of transaminase and serum creatinine levels, and decreases in neutrophil counts have also been observed (6,30,31).

The rationale for developing selective JAK-1 inhibitors such as ABT-494 is to minimize the dose-limiting side effects of pan-JAK inhibition, such as infections and anemia, which presumably occur due to inhibition of multiple isoforms of JAKs, while maintaining or increasing efficacy through selectively inhibiting JAK-1. In the current study, a broad range of doses of ABT-494 was tested to assess the safety and efficacy of ABT-494 in vivo. Overall, ABT-494 demonstrated a safety and tolerability profile consistent with observations of other JAK inhibitors tested in patients with RA. There were no serious infections, although the proportion of overall infections was higher at the 2 highest doses of ABT-494 (12 mg and 18 mg).

There was a dose-dependent reduction in hemoglobin levels. At the 12 mg and 18 mg doses, there was a modest decrease in mean hemoglobin levels by week 12, although the mean hemoglobin levels remained within the normal range. However, with higher exposures, the selectivity for JAK-1 over JAK-2 in vivo may have been reduced, as there were more cases of hemoglobin reduction at higher doses than at lower doses.

Circulating NK cells, which function as a critical mediator of host immunity against malignancy and infections, were measured as a pharmacodynamic readout of IL-15 inhibition; IL-15 is required for NK cell homeostasis. With increasing doses of ABT-494, there

was a greater mean percent decrease in NK cell counts. At the maximally efficacious dose in this population, 12 mg, NK cells decreased by 28% from baseline, with proportionally smaller decreases in NK cells observed at lower doses. Given the fact that IL-15 signaling involves a heterodimer of JAK-1 and JAK-3, this was to be expected at higher doses of ABT-494. It is unclear how much each of the heterodimeric components (JAK-1 and JAK-3) contributes to overall IL-15 signaling. However, it is possible that at higher exposure to ABT-494, the threshold for in vivo selectivity for JAK-1 compared with JAK-3 is lower in the context of the JAK-1/JAK-3 heterodimer. The significance of NK cell reduction, especially what is considered a clinically meaningful reduction in NK cells for predicting clinical events (i.e., onset of viral reactivation), is currently unknown. A significant association between decreasing nadir NK cell counts and treated infection rates with tofacitinib treatment was observed (32). No association of reduced NK cells with onset of herpes zoster was observed in the BALANCE I study, although the sample size and event numbers were very small.

As reported with other JAK inhibitors (6,30), a dose-dependent elevation of LDL cholesterol and HDL cholesterol levels was observed with ABT-494; however, the ratio of LDL cholesterol to HDL cholesterol remained unchanged. More detailed analyses of lipid particle concentrations and compositions are underway. The mean changes in other laboratory parameters of interest (serum transaminase levels and total white blood cells, neutrophils, or lymphocytes) were not influenced by increasing doses of ABT-494, with only 1 patient discontinuing the study prematurely due to leukopenia. Overall, the impact of ABT-494 on laboratory parameters would be better evaluated in longer studies and larger study populations.

Limitations of the study included a relatively small sample size. The duration of the study was 12 weeks, which was sufficient to meet the objectives of this phase IIb study and observe the timing of onset of improvement, although it precluded the assessment of longer term outcomes. The study population was restricted to patients with intolerance or an inadequate response to anti-TNF biologic therapies, and its geographic diversity was limited, as 64% of enrolled patients were from the US.

In summary, the results of the BALANCE I phase IIb study demonstrated safety and efficacy of a selective JAK-1 inhibitor, ABT-494, in a refractory population of RA patients who had an inadequate response or intolerance to anti-TNF biologic therapies. Along with data from the companion BALANCE II study (in patients with an inadequate response to MTX) (33), these results informed the selection of doses with optimal balance of efficacy and safety for further evaluation in phase III trials. Larger phase III trials are underway to confirm the selectivity of ABT-494 against JAK-1 and to determine whether this translates to an improved benefit–risk profile across a wide spectrum of RA patients.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kremer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Kremer, Emery, Camp, Friedman, Wang, Othman, Khan, Pangan, Jungerwirth, Keystone.

Analysis and interpretation of data. Kremer, Camp, Friedman, Wang, Othman, Khan, Pangan, Jungerwirth, Keystone.

ROLE OF THE STUDY SPONSOR

AbbVie funded the study, contributed to its design, and was involved in the collection, analysis, and interpretation of the data and in the writing, review, and approval of the manuscript for publication. All authors contributed to the development of the content. All authors and AbbVie reviewed and approved the manuscript. The authors maintained control over the final content.

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