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Efficacy and Safety of ABT-494, a Selective JAK-1 Inhibitor, in a Phase IIb Study in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate

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Objective. **To evaluate the efficacy and safety of ABT-494, a selective JAK-1 inhibitor, in patients with moderate-to-severe rheumatoid arthritis (RA) and an inadequate response to methotrexate (MTX).**

Methods. **Three hundred RA patients receiving stable doses of MTX were randomly assigned equally to receive immediate-release ABT-494 at 3, 6, 12, or 18 mg twice daily, 24 mg once daily, or placebo for 12 weeks. The primary efficacy end point was the proportion of patients meeting the American College of Rheumatology 20% improvement criteria (achieving an ACR20 response) at week 12, as determined using the last observation carried forward method.**

Results. **At week 12, the proportion of ACR20 responses was higher with ABT-494 (62%, 68%, 80%, 64%, and 76% for the 3, 6, 12, 18, and 24 mg doses, respectively) than with placebo (46%) (using nonresponder imputation) ($P < 0.05$ for the 6, 12, and 24 mg doses). There was a significant dose-response relationship among all ABT-494 doses ($P < 0.001$). The proportions of patients achieving ACR50 and ACR70 responses were significantly higher for all ABT-494 doses (except the 12 mg dose for the ACR70 response) than for placebo, as were changes in the Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP). Rapid improvement was demonstrated by significant differences in ACR20 response rates and changes in the DAS28-CRP for all doses compared with placebo at week 2 (the first postbaseline visit). The incidence of adverse events was similar across groups; most were mild, and infections were the most frequent. One serious infection (community-acquired pneumonia) occurred with ABT-494 at 12 mg. There were dose-dependent increases in high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, but the LDL cholesterol:HDL cholesterol ratios were unchanged through week 12. Mean hemoglobin levels remained**

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stable at lower doses, but decreases were observed at higher doses.

Conclusion. **This study evaluated a broad range of doses of ABT-494 in RA patients with an inadequate response to MTX. ABT-494 demonstrated efficacy, with a safety and tolerability profile similar to that of other JAK inhibitors.**

JAKs are essential components of intracellular signaling pathways of various cytokines that are involved in the pathogenesis of rheumatoid arthritis (RA) (1–3). The roles of JAK-1 and JAK-2 are diverse, including host defense, hematopoiesis, growth, and neural development. JAK-3 and Tyk-2 play an essential role in immune responses (3). Inhibition of JAK-1 has been associated with reductions in proinflammatory cytokines, such as interleukin-6 (IL-6) and interferons α, β, and γ, and thereby with control of inflammation. Selective inhibition of JAK-1 might possibly enhance efficacy and reduce undesirable effects associated with inhibition of JAK-2, JAK-3, and Tyk-2. Small molecules that inhibit JAKs (including JAK-1, JAK-2, JAK-3, and Tyk-2) with varying selectivity have been approved or are currently in development for treatment of RA. Tofacitinib, which primarily inhibits JAK-3 and JAK-1 and, to a lesser extent, JAK-2, was shown to be effective in RA patients with inadequate responses to methotrexate (MTX) and anti–tumor necrosis factor (anti-TNF) agents as well as in MTX-naive RA patients (4–7), as was baricitinib, a JAK-1/2 inhibitor (8,9).

ABT-494 is currently in development to treat active RA in adult patients. ABT-494 is a JAK inhibitor with enhanced selectivity for JAK-1 compared with JAK-2 (~74-fold higher, with a 50% inhibition concentration [IC_{50}] of 8 n*M* compared with 600 n*M*, respectively) in cellular assays, and with enhanced selectivity for JAK-1 compared with JAK-3 (~58-fold higher, with an IC_{50} of 40 n*M* compared with 2.3 μ*M*, respectively) in biochemical assays (10,11). This increased selectivity potentially offers an improved benefit–risk profile in patients with RA. Herein, we present results from the 12-week dose-ranging BALANCE II study, which evaluated the safety and efficacy of immediate-release ABT-494 (3, 6, 12, and 18 mg twice daily and 24 mg once daily) versus placebo in adult patients with moderately to severely active RA who had shown an inadequate response to MTX therapy.

PATIENTS AND METHODS

Patients. Patients were eligible if they were ≥18 years of age with active RA, fulfilled either the American College of Rheumatology (ACR) 1987 revised classification criteria (12) or the ACR/European League Against Rheumatism 2010 classification criteria (13) for ≥3 months, and had active disease despite treatment with MTX. Active disease was defined as having ≥6 swollen joints (based on a 66-joint count) and ≥6 tender joints (based on a 68-joint count) and either a high-sensitivity C-reactive protein (hsCRP) level greater than the upper limit of normal (ULN) (5 mg/liter) or seropositivity for both rheumatoid factor and anti–cyclic citrullinated peptide. Eligible patients had been receiving MTX for ≥3 months, with a stable dose (7.5–25 mg/week) for ≥4 weeks (maximum tolerated dose after complete titration) before baseline. All other oral disease-modifying antirheumatic drugs (DMARDs) had to be discontinued for a prespecified duration before baseline to ensure appropriate washout. All patients either had a negative tuberculosis screening assessment or, if assessments indicated latent tuberculosis infection, had completed at least 2 weeks of ongoing tuberculosis prophylaxis or had documented completion of a full course of tuberculosis prophylaxis before baseline. Patients were excluded if they had received JAK inhibitor therapy or any other investigational or approved biologic RA therapy.

Study design. BALANCE II was a phase IIb, 12-week, randomized, double-blind, parallel-group, placebo-controlled study initiated in March 2014, with the last patient completing the study in July 2015. The study was conducted at 63 sites, 59 of which enrolled patients. Geographic regions were defined as Eastern Europe (Bulgaria, the Czech Republic, Hungary, Latvia, Poland, Russia, Slovakia, Turkey, and Ukraine), Latin/South America (including Chile and Mexico), Western Europe (Spain), the United States, Israel, Puerto Rico, and South Africa.

Treatment. Patients were randomly assigned 1:1:1:1:1:1 in a double-blinded manner to receive immediate-release oral doses of ABT-494 at 3 mg, 6 mg, 12 mg, or 18 mg twice daily, or 24 mg once daily, or placebo twice daily for 12 weeks, using an interactive voice/web response system according to a blocked randomization schedule generated by the AbbVie statistics department. Investigators, patients, and other study personnel were blinded to treatment assignments throughout the study. Patients continued their stable dose of background MTX during the study and were to take a dietary supplement of oral folic acid (or equivalent) from 4 weeks before baseline and during the study. Concurrent treatment was permitted with stable doses of other, non-DMARD background RA therapy, including nonsteroidal antiinflammatory drugs, acetaminophen, oral corticosteroids (equivalent to prednisone at ≤10 mg/day), and low-potency opiates. Patients who completed the 12-week randomized controlled study completed a 30-day follow-up visit or had the option to enter an open-label extension study.

The study was conducted according to the guidelines of the International Conference on Harmonisation, applicable regulations and guidelines governing clinical study conduct, and the Declaration of Helsinki. All study-related documents were reviewed and approved by independent ethics committees and institutional review boards. All patients provided written informed consent before participating in study-related procedures.

Efficacy assessments. The primary end point was the proportion of patients who met the ACR 20% improvement criteria (achieved an ACR20 response) (14) at week 12. Secondary end points included the proportions of patients achieving ACR50 and ACR70 responses at week 12, the proportion of patients achieving a Disease Activity Score in 28 joints (15) using the CRP level (DAS28-CRP) of ≤3.2 or <2.6 at week 12, and the proportion of patients achieving low disease activity or clinical remission based on Clinical Disease Activity Index (CDAI) (16) criteria (CDAI score ≤10 indicates low disease activity; CDAI score ≤2.8 indicates clinical remission). We also assessed improvements in individual components of the ACR core set of

Table 1. Baseline demographic and disease characteristics of the RA patients with an inadequate response to MTX in the modified intent-to-treat population*

		ABT-494				
	Placebo (n = 50)	3 mg twice daily (n = 50)	6 mg twice daily (n = 50)	12 mg twice daily (n = 50)	18 mg twice daily (n = 50)	24 mg once daily (n = 49)
Demographic characteristics						
Age, years	55 ± 12	53 ± 12	55 ± 12	56 ± 12	55 ± 14	56 ± 12
Years since RA diagnosis	5.9 ± 5.3	3.9 ± 3.8	7.0 ± 5.5	9.3 ± 8.6	7.3 ± 7.9	8.3 ± 7.1
Women, no. (%)	38 (76)	40 (80)	34 (68)	41 (82)	42 (84)	42 (86)
RF positive, no. (%)	41 (82)	45 (90)	46 (92)	44 (88)	41 (82)	44 (90)
Anti-CCP positive, no. (%)	39 (78)	40 (80)	45 (90)	43 (86)	40 (80)	45 (92)
MTX dose, mg/week	16 ± 4	16 ± 4	16 ± 4	14 ± 4	15 ± 5	15 ± 4
Receiving prednisone, no. (%)	8 (16)	10 (20)	16 (32)	16 (32)	6 (12)	5 (10)
Previous non-MTX DMARDs, no. (%)	7 (14)	6 (12)	12 (24)	11 (22)	5 (10)	12 (24)
1	6 (12)	4 (8)	10 (20)	9 (18)	2 (4)	8 (16)
2	1 (2)	2 (4)	1 (2)	1 (2)	1 (2)	3 (6)
≥3	0	0	1 (2)	1 (2)	2 (4)	1 (2)
Disease characteristics						
PtGA, 0–100-mm VAS	62 ± 19	60 ± 24	61 ± 18	59 ± 22	63 ± 19	65 ± 20
Patient's assessment of pain, 0–100-mm VAS	60 ± 19	60 ± 22	62 ± 19	63 ± 22	66 ± 16	67 ± 20
PhGA, 0–100-mm VAS	62 ± 15	62 ± 17	63 ± 19	60 ± 16	65 ± 15	67 ± 15
TJC of 68 joints	29 ± 16	27 ± 15	28 ± 16	28 ± 13	27 ± 15	28 ± 16
TJC of 28 joints	16 ± 8	15 ± 8	17 ± 8	16 ± 7	16 ± 7	15 ± 7
SJC of 66 joints	19 ± 12	15 ± 8	19 ± 12	17 ± 11	17 ± 12	18 ± 13
SJC of 28 joints	12 ± 6	11 ± 5	13 ± 6	12 ± 6	12 ± 6	12 ± 6
HAQ DI score, range 0–3	1.4 ± 0.7	1.3 ± 0.7	1.6 ± 0.7	1.5 ± 0.6	1.6 ± 0.6	1.5 ± 0.7
DAS28-CRP	5.6 ± 1.1	5.5 ± 1.1	5.8 ± 1.0	5.6 ± 0.9	5.7 ± 0.8	5.7 ± 1.0
CDAI score	40 ± 14	38 ± 13	43 ± 14	39 ± 12	40 ± 13	41 ± 13
hsCRP level, mg/liter	15 ± 26	11 ± 15	17 ± 20	11 ± 15	13 ± 15	14 ± 16
hsCRP level >ULN, no. (%)†	27 (54)	25 (50)	31 (62)	26 (52)	28 (56)	33 (67)

* Except where indicated otherwise, values are the mean ± SD. RA = rheumatoid arthritis; MTX = methotrexate; DMARDs = disease-modifying antirheumatic drugs; PtGA = patient's global assessment of disease activity; VAS = visual analog scale; PhGA = physician's global assessment of disease activity; TJC = tender joint count; SJC = swollen joint count; 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.

† The upper limit of normal (ULN) is 5 mg/liter. Patients with normal levels of high-sensitivity CRP (hsCRP) could be enrolled if they were positive for rheumatoid factor (RF) and anti–cyclic citrullinated peptide (anti-CCP).

disease activity measures (17), change in the DAS28-CRP, change in the CDAI score over 12 weeks, and the proportion of patients achieving a minimum clinically important difference (MCID) of −0.22 on the Health Assessment Questionnaire disability index (HAQ DI) (18,19) at week 12. Changes in the Simplified Disease Activity Index (SDAI) (20) and in the proportion of patients who had an ACR20 response at every visit (at weeks 2, 4, 6, 8, and 12) were calculated post hoc.

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 (14% of week 12 samples). We performed sensitivity analyses on the affected samples using a larger-than-expected correction factor (20% inflation) (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 assessments. Adverse events (AEs), vital signs, physical examination findings, and laboratory test results were evaluated at each scheduled visit during treatment and for 30 days after the last dose of study drug. Coding of AEs was based on the Medical Dictionary for Regulatory Activities, version 17.1. AE severity and postbaseline changes in laboratory test results were described according to The Rheumatology Common Toxicity Criteria, version 2.0, developed by the Outcome Measures in Rheumatology Drug Safety Working Group (21). An independent Cardiovascular Adjudication Committee was used for blinded assessment of potential cardiovascular AEs.

Statistical analysis. All efficacy analyses were conducted in the modified intent-to-treat population, which consisted of all randomized patients who had received at least 1 dose of study drug. The last observation carried forward (LOCF) method was used as the primary missing data imputation method for ACR response rates. Efficacy results were further assessed using nonresponder imputation (NRI), and these data are also presented. LOCF missing data imputation was used for continuous end points such as the DAS28-CRP, while 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 used 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. A sample of 270 patients (45 per randomized treatment group) was targeted to give 80% power to detect a difference of 30% in the primary efficacy end point (ACR20 response rate at week 12), assuming that the response rate would be 30% in the placebo group and 60% in at least 1 of the ABT-494 dose groups.

RESULTS

Patient disposition and baseline characteristics. Three hundred patients were randomized, and 299 patients received at least 1 dose of either placebo (n = 50) or immediate-release ABT-494 at 3 mg (n = 50), 6 mg (n = 50), 12 mg (n = 50), or 18 mg (n = 50) twice daily, or 24 mg once daily (n = 49). Patients were from Eastern Europe (61%), Latin/South America (18%), the United States (10%), Western Europe (8%), or other regions (4%). In general, demographic and clinical characteristics at baseline were similar among treatment groups (Table 1). The mean ± SD duration since disease diagnosis was 6.9 ± 6.7 years, 17.7% had previously used at least 1 non-MTX DMARD, and the mean ± SD MTX dose was 15.2 ± 4.2 mg/week. Mean ± SD swollen and tender joint counts at baseline were 17.5 ± 11.5 (of 66 joints) and 27.8 ± 15.5 (of 68 joints), respectively. The mean ± SD DAS28-CRP was 5.7 ± 1.0. Fifty-seven percent of patients had elevated CRP levels at baseline. Overall, 91% of patients completed the study, with similar discontinuation rates across treatment groups and no apparent relationship between ABT-494 dose and discontinuation (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39808/abstract).

Efficacy. The proportion of ABT-494–treated patients achieving an ACR20 response at week 12 (by the LOCF method) was significantly higher than the corresponding proportion of placebo-treated patients (50%) for all except those receiving the lowest dose of 3 mg twice daily (65% for 3 mg twice daily, $P = 0.153$; 73% for 6 mg twice daily, $P = 0.018$; 82% for 12 mg twice daily, $P = 0.001$; 77% for 18 mg twice daily, $P = 0.008$; 82% for 24 mg once daily, $P = 0.001$). Using NRI, the proportions of patients achieving an ACR20 response at week 12 were significantly higher with ABT-494 at 6 mg twice daily (68%), 12 mg twice daily (80%), and 24 mg once daily (76%) than with placebo (46%), and numerically higher than placebo for those receiving 3 mg twice daily (62%) and 18 mg twice daily (64%) (Figure 1). A significant dose-response relationship was identified ($P < 0.001$ for all doses). At week 12, ACR50 and ACR70 responses were achieved by significantly higher percentages of patients who received ABT-494 versus those who received placebo at all doses except 12 mg twice daily for the ACR70 response (by NRI) (Figure 1).

At the first study visit assessment (week 2), ACR20 responses with ABT-494 ranged from 30% to 44% and

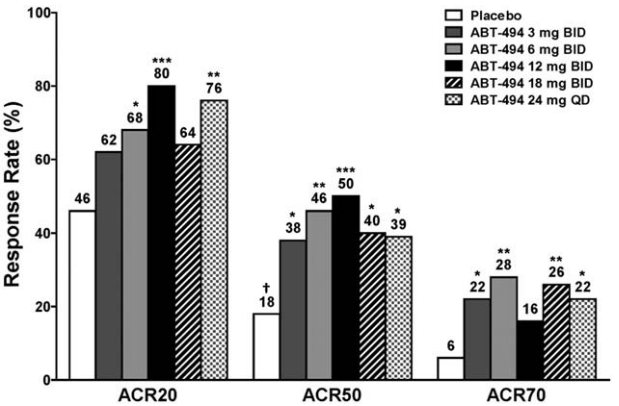

Figure 1. Proportion of patients with rheumatoid arthritis meeting the American College of Rheumatology criteria for 20% improvement (ACR20), 50% improvement, and 70% improvement at week 12 of treatment with ABT-494 (modified intent-to-treat population; nonresponder imputation analysis). † = The sensitivity analysis for correction of affected high-sensitivity C-reactive protein samples demonstrated that there was a potential shift of 1 patient from responder to nonresponder in the placebo arm for ACR50 response (from 18% down to 16%). * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$ versus placebo. BID = twice daily; QD = once daily.

were significantly higher at all doses ($P < 0.05$) compared with placebo (12%) (by NRI) (Figure 2A). The proportion of ACR20 responses increased over time with ABT-494 and reached maximum values between weeks 6 and 12. Likewise, significantly more patients receiving ABT-494 than those receiving placebo had an ACR50 response from week 4 onward (by NRI), except for the 24 mg dose at 6 weeks (Figure 2B). Significantly more patients receiving ABT-494 than those receiving placebo achieved ACR70 responses by week 6, with some further improvements up to week 12 (by NRI) (Figure 2C). Twenty-four percent of patients receiving ABT-494 at 12 mg twice daily maintained an ACR20 response at every visit from week 2 through week 12 (see Supplementary Figure 2, http://onlinelibrary.wiley.com/doi/10.1002/art.39808/abstract). Mean decreases from baseline in the DAS28-CRP increased over time for all ABT-494 doses, and improvements were significantly higher compared with placebo at every time point. By week 12, improvement from baseline in the DAS28-CRP with ABT-494 ranged from −2.2 to −2.6 versus −1.3 for placebo (Figure 2D). Improvements from baseline in CDAI scores were consistent with improvements in the DAS28-CRP, and by week 8, improvements in CDAI scores were significantly higher at doses of ≥6 mg twice daily (see Supplementary Figure 3B, http://onlinelibrary.wiley.com/doi/10.1002/art.39808/abstract). The CDAI and SDAI scores, hsCRP level, and DAS28-CRP are presented in Supplementary Figures 3A, C, E, and F.

At week 12, significantly higher percentages of patients treated with all doses of ABT-494 (41–52%) than those treated with placebo (20%) achieved a DAS28-CRP

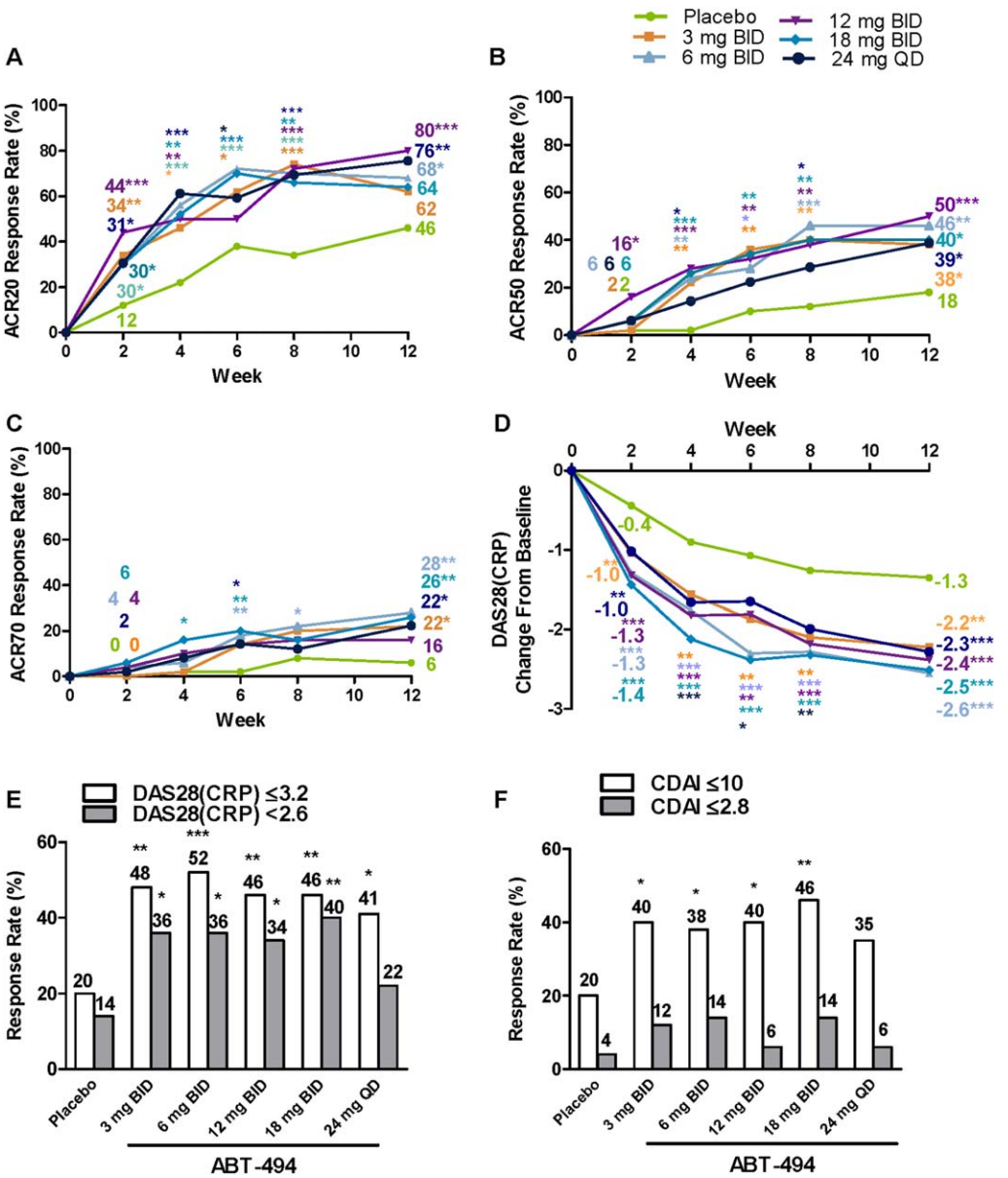

Figure 2. **A–C,** Proportions of patients achieving ACR20 responses (**A**), ACR50 responses (**B**), and ACR70 responses (**C**) over 12 weeks (modified intent-to-treat [ITT] population; nonresponder imputation [NRI] analysis). **D,** Mean change in Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) from baseline through 12 weeks (modified ITT population; observed patients). **E** and **F,** Proportion of patients achieving a DAS28-CRP of ≤3.2 or <2.6 (**E**) or low disease activity or clinical remission based on Clinical Disease Activity Index (CDAI) criteria (CDAI score ≤10 indicates low disease activity; CDAI score ≤2.8 indicates clinical remission) (**F**) at week 12 of treatment with ABT-494 (modified ITT population; NRI analysis). * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$ versus placebo. See Figure 1 for other definitions.

of ≤3.2. A DAS28-CRP of <2.6 was achieved by significantly higher percentages of patients treated with ABT-494 (34–40%) than those treated with placebo (14%) at all doses except 24 mg once daily (22%) (by NRI) (Figure 2E). Similarly, at week 12, low disease activity according to the CDAI score was achieved by a significantly higher percentage of patients receiving ABT-494 (40–46%) than those receiving placebo (20%) at all doses except 24 mg once daily (35%) (by NRI) (Figure 2F). A slightly lower percentage of patients achieved low disease activity according to the CDAI score than the percentage who achieved a DAS28-CRP of ≤3.2, and fewer patients achieved clinical remission according to the CDAI score than achieved a DAS28-CRP of <2.6.

Improvements from baseline in all the individual components of the ACR core set of disease activity measures were greater with ABT-494 than with placebo, reaching statistical significance for most comparisons at doses of ≥6 mg twice daily (Table 2). Changes from

Table 2. Comparison of ABT-494 with placebo at week 12 for changes from baseline in disease activity measures of the American College of Rheumatology core set in the modified intent-to-treat population using last observation carried forward imputation of missing values*

		ABT-494				
	Placebo (n = 47)	3 mg twice daily (n = 49)	6 mg twice daily (n = 49)	12 mg twice daily (n = 50)	18 mg twice daily (n = 49)	24 mg once daily (n = 49)
Patient's assessment of pain	−19.9 (−26.5, −13.4)†	−25.3 (−31.7, −19.0)	−33.8 (−40.1, −27.4)‡	−33.4 (−39.6, −27.1)‡	−34.9 (−41.4, −28.4)‡§	−29.8 (−36.1, −23.4)¶
PhGA	−28.0 (−33.3, −22.6)§	−34.7 (−39.9, −29.6)	−43.0 (−48.2, −37.9)†#	−45.6 (−50.8, −40.5)#	−36.6 (−41.8, −31.3)§¶	−37.4 (−42.9, −32.3)¶**
PtGA	−17.5 (−24.5, −10.5)†	−26.9 (−33.6, −20.1)	−31.4 (−38.1, −24.6)#	−23.8 (−30.5, −17.2)	−29.1 (−35.9, −22.2)§¶	−24.1 (−30.9, −17.4)
TJC of 68 joints	−14.4 (−17.6, −11.1)	−15.9 (−19.1, −12.8)	−19.2 (−22.4, −16.1)¶	−19.2 (−22.3, −16.1)¶	−17.4 (−20.6, −14.3)	−18.8 (−22.0, −15.6)
SJC of 66 joints	−10.0 (−11.8, −8.2)	−12.0 (−13.8, −10.3)	−11.9 (−13.7, −10.2)	−12.7 (−14.4, −10.9)¶	−13.2 (−15.0, −11.5)¶	−13.0 (−14.7, −11.2)¶
HAQ DI score, range 0–3	−0.4 (−0.5, −0.2)§	−0.6 (−0.8, −0.5)¶	−0.7 (−0.8, −0.5)‡	−0.8 (−0.9, −0.6)#	−0.6 (−0.7, −0.4)§¶	−0.6 (−0.7, −0.4)
HAQ DI score ≥MCID, no. (%)/(95% CI)††	30 (67)/(53, 80)	33 (67)/(54, 81)	34 (69)/(57, 82)	44 (88)/(79, 97)	35 (74)/(62, 87)	38 (78)/(66, 89)
hsCRP, mg/liter	−0.4 (−3.5, 2.6)	−10.5 (−13.5, −7.6)#	−8.8 (−11.8, −5.8)#	−8.9 (−11.9, −5.9)#	−7.5 (−10.5, −4.6)‡	−8.4 (−11.4, −5.5)#

* Except where indicated otherwise, values are the mean change (95% confidence interval [95% CI]); 95% CIs were calculated based on a normal approximation to the binomial distribution. PhGA = physician's global assessment of disease activity; PtGA = patient's global assessment of disease activity; TJC = tender joint count; SJC = swollen joint count; hsCRP = high-sensitivity C-reactive protein.
† Data were missing for 1 patient.
‡ $P < 0.01$ versus placebo.
§ Data were missing for 2 patients.
¶ $P < 0.05$ versus placebo.
# $P < 0.001$ versus placebo.
** Data were missing for 3 patients.
†† The minimum clinically important difference (MCID) for the Health Assessment Questionnaire disability index (HAQ DI) score was −0.22.

baseline in the HAQ DI score at week 12 with ABT-494 ranged from −0.6 to −0.8 and were significantly greater than those with placebo (−0.4) for all but the dose of 24 mg once daily (−0.6). Compared with patients receiving placebo (67%), a numerically greater proportion of patients receiving ABT-494 at ≥6 mg twice daily (69–88%) met the MCID for the HAQ DI score at week 12.

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 patient from responder to nonresponder in the placebo arm for ACR50 response (from 18% down to 16%). Overall, the study showed a tendency toward geographic differences in responses across the treatment arms, with a trend toward higher responses observed in countries in Eastern Europe, Latin America, and South America (see Supplementary Table 1, http://onlinelibrary.wiley.com/doi/10.1002/art.39808/abstract).

Safety. The overall incidence of treatment-emergent AEs was higher with ABT-494 than with placebo (45% versus 26%), with a trend toward higher incidences of AEs at higher doses (Table 3). Most reported AEs were mild in severity. Ten patients discontinued ABT-494 or placebo due to an AE (dyspepsia in the placebo group; headache in the 3 mg group; mood swings in the 6 mg group; pneumonia in the 12 mg group; hyperbilirubinemia, pyrexia, decreased hemoglobin, decreased neutrophil count, and decreased white blood cell count in the 18 mg group; and abdominal pain in the 24 mg group). Infections were the most common AEs reported during the trial. Three events of herpes zoster were reported with ABT-494 (1 at 3 mg and 2 at 24 mg); each involved a single dermatome. All were mild-to-moderate in severity and considered nonserious by the investigator. Among the most commonly observed AEs (defined as having occurred in ≥5% of patients in any dose group) were nasopharyngitis, headache, increased blood creatine phosphokinase (CPK), diarrhea, back pain, cough, influenza, leukopenia, and dyslipidemia.

Eight patients in the ABT-494 treatment groups and none in the placebo group experienced serious AEs (SAEs). At 6 mg, 2 patients experienced an SAE (1 had osteonecrosis and 1 had lung cancer). The patient with lung cancer was a

Table 3. Safety data through week 12 in the safety analysis population*

		ABT-494				
	Placebo (n = 50)	3 mg twice daily (n = 50)	6 mg twice daily (n = 50)	12 mg twice daily (n = 50)	18 mg twice daily (n = 50)	24 mg once daily (n = 49)
Overall AEs						
Any AE	13 (26)	20 (40)	23 (46)	29 (58)	25 (50)	17 (35)
Any SAE	0	0	2 (4)	1 (2)	3 (6)	2 (4)
Any severe AE	0	0	1 (2)	1 (2)	1 (2)	1 (2)
Any AE leading to discontinuation	1 (2)	1 (2)	1 (2)	1 (2)	5 (10)	1 (2)
Any death†	0	0	0	0	0	0
AEs of special interest						
Infection	7 (14)	10 (20)	7 (14)	12 (24)	11 (22)	9 (18)
Serious infection	0	0	0	1 (2)	0	0
Cardiovascular event	0	0	0	1 (2)‡	0	0
Herpes zoster§	0	1 (2)	0	0	0	2 (4)
Hepatic disorder	0	1	0	0	2 (4)	0
Malignancy	0	0	1 (2)†	0	0	0

* Values are the number (%) of patients. AEs = adverse events; SAE = serious AE.
† Lung cancer on posttreatment day 10 in a 79-year-old man who had smoked for 40 years and had a family history of lung cancer; the patient died 3 months later.
‡ Cerebrovascular accident adjudicated as an ischemic stroke.
§ Events involved 1 dermatome in each patient.

79-year-old man who had smoked for 40 years and had a family history of lung cancer; lung cancer was diagnosed on posttreatment day 10, and the patient died 3 months later. At 12 mg, 1 patient experienced an SAE of pneumonia that led to early discontinuation. At 18 mg, 3 patients experienced an SAE (sciatica, ovarian cyst, and pyrexia in 1 patient each), and at 24 mg, 2 patients experienced 3 SAEs (syncope and head injury in 1 patient, and forearm fracture in 1 patient). One adjudicated cardiovascular event was reported during the study (a nonserious event of ischemic stroke at 12 mg in a patient with transient difficulty in speech and history of cerebral infarction). No patient in any treatment group reported an opportunistic infection, nonmelanoma skin cancer, or gastrointestinal (GI) perforation. There were no deaths reported during the trial, although the patient diagnosed as having lung cancer on posttreatment day 10 died 3 months after completing the study.

At week 12, treatment with ABT-494 led to modest increases in mean values for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) compared with placebo; no clear dose dependence was observed for either increase (see Supplementary Tables 2 and 3, http://onlinelibrary.wiley.com/doi/10.1002/art.39808/abstract). Grade 3 or grade 4 ALT or AST abnormalities during the study were infrequent, with 3 patients experiencing a grade 3 AST abnormality, 4 patients experiencing a grade 3 ALT elevation, and 1 patient experiencing a grade 4 ALT elevation. None of these led to study discontinuation. There were no grade 3 or grade 4 elevations observed for creatinine during the study (see Supplementary Table 3). At week 12, mean creatinine and CPK levels were higher in all ABT-494 dose groups compared with placebo, but these were not considered clinically significant. Six patients treated with ABT-494 had CPK elevations $>4\times$ ULN, but these were not dose dependent. All 6 patients were asymptomatic, and values returned to normal or pretreatment levels with continued ABT-494 treatment. No patient discontinued the study due to these CPK elevations. ABT-494 was associated with elevations in high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol across all tested doses at week 12 compared with placebo; however, the LDL cholesterol:HDL cholesterol ratios remained consistent through week 12.

Although decreases in lymphocyte and neutrophil counts were observed with ABT-494 treatment, no statistically significant decline in mean lymphocyte or neutrophil counts relative to placebo were observed for any ABT-494 dose groups by week 12. Two patients had grade 4 reductions in lymphocytes (1 in the 3 mg group and 1 in the 18 mg group) (see Supplementary Table 3, http://onlinelibrary.wiley.com/doi/10.1002/art.39808/abstract); the patient in the 18 mg group reported an event of skin infection during the study, which was not reported in temporal proximity to the lymphocyte decrease. There were no grade 4 neutrophil reductions in any of the treatment groups. A dose-dependent decrease in natural killer (NK) cells (CD3−CD16+CD56+) was observed in patients treated with ABT-494 at $\geq$6 mg (22) (see Supplementary Figure 4, http://onlinelibrary.wiley.com/doi/10.1002/art.39808/abstract). The mean ± SD change in NK cells was 2.3 ± 40.9% in the placebo group and 1.9 ± 47.8%, −13.3 ± 44.1%,

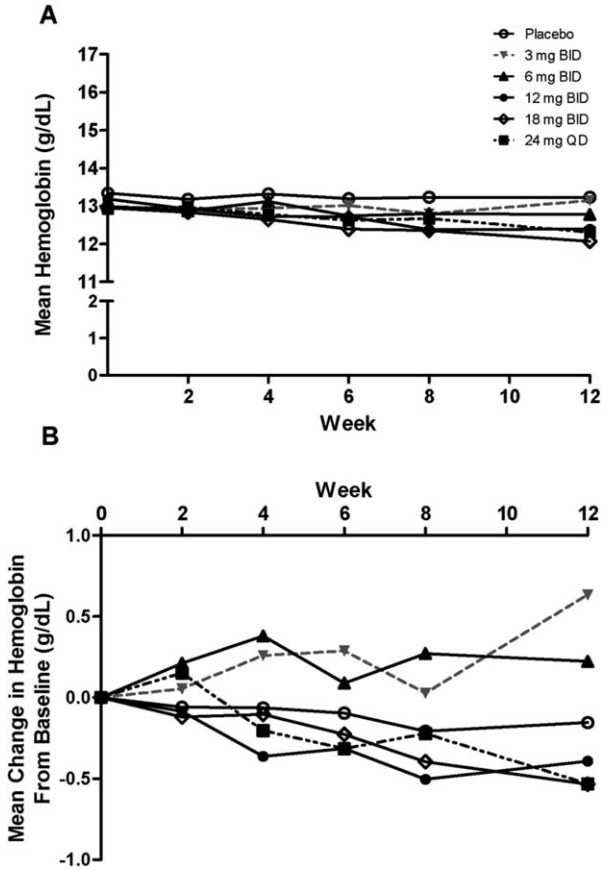

Figure 3. **A,** Mean hemoglobin levels over 12 weeks in all patients. **B,** Mean change in hemoglobin levels from baseline over 12 weeks in patients with high-sensitivity C-reactive protein levels of >5 mg/liter at baseline. The normal range for hemoglobin is 13.2–17.0 gm/dl in males and 11.5–15.5 gm/dl in females. Shown are observed data from the safety population. See Figure 1 for definitions.

$-23.8 \pm 59.5\%$, $-46.1 \pm 28.0\%$, and $-39.9 \pm 39.0\%$ in the 3, 6, 12, 18, and 24 mg groups, respectively ($P \leq 0.01$ for 12 mg, 18 mg, and 24 mg).

Mean hemoglobin values remained stable or increased at lower doses (3 mg and 6 mg), most notably in patients with elevated hsCRP at baseline (Figures 3A and B). Dose-dependent decreases in hemoglobin were seen at higher doses (12 mg, 18 mg, and 24 mg). One patient in the 18 mg group discontinued the study due to decreased hemoglobin (from 14.4 gm/dl at baseline to 10.7 gm/dl at week 11).

DISCUSSION

Differences in selectivity of JAK inhibitors for the members of the JAK family may be associated with an improved benefit–risk profile in a number of autoimmune diseases. ABT-494 is a novel, selective JAK-1 inhibitor designed to inhibit JAK-1 with greater potency than it inhibits JAK-2 and JAK-3. The BALANCE II study investigated a broad range of doses, as well as once and twice daily dosing schedules, of immediate-release ABT-494 to assess its efficacy and safety for the treatment of RA in patients with an inadequate response to stable MTX therapy.

Clinical efficacy of ABT-494 was demonstrated with the primary efficacy end point of an ACR20 response being met at all doses at week 12, as assessed by the LOCF method and at the 6, 12, and 24 mg doses when assessed by NRI. Similarly, efficacy of ABT-494 treatment was demonstrated for the secondary efficacy end points. Onset of improvement was rapid, as demonstrated by the achievement of ACR20 responses by 30–44% of patients treated with ABT-494 at week 2. Improvements were also sustained, with 18–24% of patients receiving ABT-494 meeting the ACR20 response criteria at all visits from week 2 through week 12. Likewise, looking at measures of a greater magnitude of response, such as the ACR50 and ACR70, significant differences for most doses of ABT-494 versus placebo were observed early during the study, with maximum improvement achieved between weeks 6 and 12. Low levels of disease activity as measured by the DAS28-CRP were achieved in nearly half of the patients receiving ABT-494 by week 12. For all efficacy measures, a clear dose-response relationship was observed across the tested doses, with maximum efficacy reached at doses of 6 or 12 mg. The underreporting of a minority of hsCRP values was predicted to have no significant impact on efficacy parameters and the overall conclusions from the study.

Similar to findings with biologic therapies currently used for the treatment of RA, infections were the most common AEs. Three nonserious events of herpes zoster were reported with ABT-494 (1 at 3 mg and 2 at 24 mg), each involving a single dermatome. There were no reports of opportunistic infection, nonmelanoma skin cancer, or GI perforation. No deaths occurred during the study. There were no unexpected AE trends based on the known safety of drugs from the same class. Safety observations from this phase IIb study support proceeding to larger phase III trials in which the safety profile will be further characterized and confirmed.

Consistent with observations for other JAK inhibitors and drugs that inhibit IL-6 (5,9,23), certain effects on laboratory parameters were also observed with ABT-494 and are likely to be attributable to potent JAK-1 inhibition (3,24). Treatment with ABT-494 was associated with elevations in liver enzymes, LDL and HDL cholesterol, and CPK, with no apparent dose relationship. Although increases in LDL and HDL cholesterol were observed across all tested doses, the LDL cholesterol:HDL cholesterol ratios remained consistent throughout. Liver enzyme

elevations were infrequent and usually transient, while CPK elevations were asymptomatic and returned to normal levels with continued treatment.

Inhibition of IL-6 signaling activity has previously been shown to be associated with decreased levels of the iron-sequestering hormone, hepcidin, and CRP, and with increased levels of hemoglobin (25,26). In the subgroup of patients with elevated hsCRP at baseline, mean hemoglobin values increased over time for the 3 mg and 6 mg groups, while decreases in hemoglobin were observed at doses of ≥12 mg, with limited clinical impact. This observation is possibly due to higher selectivity of ABT-494 for JAK-1 over JAK-2 at lower doses combined with reduced systemic inflammation, leading to an improvement in hemoglobin levels. These findings suggest that ABT-494 is selective for JAK-1 at lower doses and less selective at higher doses. This was taken into consideration in the analysis of the efficacy and safety data to determine the optimal doses to take forward into phase III studies.

Reductions in lymphocytes and neutrophils were observed during treatment with ABT-494, with higher incidences of grade 3 or 4 reductions in lymphocytes reported at higher doses; however, only 1 patient with a grade 4 reduction ($<0.5 \times 10^9$/liter) in lymphocytes had a skin infection, which was not reported in temporal proximity to the lymphocyte decrease. No grade 4 neutrophil reductions were reported.

Compared with placebo, there were also reductions in NK cells observed at ABT-494 doses of ≥6 mg, similar to observations with other compounds of the same class (27,28). The relevance of NK cell reduction to predicting clinical events, such as viral reactivation, is unclear. No association of reduced NK cells with herpes zoster events was observed, although the sample size was small. The potential correlation of NK cell reductions with safety of ABT-494 treatment needs to be further investigated in larger phase III trials.

Limitations of the study include the overall length and size of a phase IIb dose-ranging study. The placebo control was limited to 12 weeks due to ethical concerns about extending placebo control in patients with active disease, while the size was restricted to ~50 patients per individual dosing arm. However, patients completing the 12 weeks of treatment in this study had the option to continue into a long-term extension study. The study enrolled patients with an inadequate response to MTX, which limited the ability to extrapolate the efficacy and safety results of this study to other populations. The companion study, BALANCE I (22), included patients with active RA for whom at least 1 anti-TNF or biologic therapy had failed. Dose dependence in the achievement of some clinical responses was not always apparent, possibly due to the 12-week time frame and small patient numbers in this phase IIb trial. These effects are better evaluated in larger phase III trials, which include a broader patient population and a longer time frame.

The observed placebo response in BALANCE II was higher than previously reported for RA trials conducted several years prior to this study. In the placebo group, 46% of patients achieved an ACR20 response at week 12, with a clear regional variance in response contributing to this effect, which may reflect the tendency toward increasing placebo responses as demonstrated by contemporaneous clinical trials in this group (9,29–31) (see Supplementary Table 1, http://onlinelibrary.wiley.com/doi/10.1002/art.39808/abstract). Regional differences in patients' expectations and perceptions of treatment efficacy may contribute to the trend recently observed in RA clinical trials and may reflect patients' attitudes toward more advanced treatment. Despite the high placebo response observed, ABT-494 showed statistically significant and clinically meaningful differences from placebo at most doses.

In conclusion, this study demonstrated that selective JAK-1 inhibition with ABT-494 was effective in patients with active RA and an inadequate response to MTX who were receiving stable background MTX. ABT-494 demonstrated a safety and tolerability profile consistent with other JAK inhibitors tested in RA. Together with BALANCE I (22), the BALANCE II study evaluated a broad range of ABT-494 doses in order to understand the boundaries of safety and efficacy. Doses that reflect the optimal benefit–risk profile will be evaluated in phase III studies to confirm the safety and efficacy observed in this study and will allow comprehensive characterization of the clinical and pharmacologic profile of ABT-494.

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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. Genovese 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.

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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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