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Response to baricitinib therapy in patients with rheumatoid arthritis with inadequate response to csDMARDs as a function of baseline characteristics

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ABSTRACT

Objective We analysed the effects of baseline characteristics on the safety and efficacy of baricitinib in patients with rheumatoid arthritis (RA) with inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) from two phase III trials.

Methods In RA-BEAM (NCT01710358), patients with inadequate response to methotrexate were randomised to placebo, baricitinib 4 mg or adalimumab 40 mg. RA-BUILD (NCT01721057) patients had inadequate response to ≥1 csDMARDs and were randomised to either placebo or once-daily baricitinib (2 or 4 mg). Both study populations were naïve to biologic DMARDs (bDMARDs). Primary end point for both studies was American College of Rheumatology 20% improvement (ACR20) response at week 12. Pooled data from the two trials were analysed post hoc based on select subgroups defined by age, previous csDMARD use, baseline RA disease activity, etc, with assessment of clinical and safety outcomes at week 12 and radiographic outcomes at week 24 for the baricitinib 4 mg and placebo-treated patients.

Results Efficacy was observed with baricitinib 4 mg treatment irrespective of patient demographics and baseline disease characteristics. ORs primarily favoured baricitinib over placebo in the ACR20 response. In other outcomes such as Disease Activity Score for 28 joints based on high-sensitivity C reactive protein levels, Simplified Disease Activity Index score ≤11 and radiographic progression, baricitinib 4 mg showed better responses than placebo regardless of baseline characteristics. Safety events were more common in patients over 65 years, but similar between baricitinib 4 mg and placebo patients.

Conclusion Baseline characteristics did not substantially affect clinical response to baricitinib 4 mg in patients with RA with inadequate response to csDMARDs.

Key messages

What is already known about this subject?

- Baricitinib, an oral selective Janus kinase (JAK)1/JAK2 inhibitor, has shown beneficial treatment effect in patients with moderate-to-severe rheumatoid arthritis with inadequate response to conventional synthetic DMARDs.

What does this study add?

- This analysis demonstrates that it is impossible to identify a subset of patients is likely to benefit from baricitinib therapy, or a subset of patients that is unlikely to respond.
- Patient demographics and baseline disease characteristics do not have a substantial effect on patients' response to treatment with baricitinib.

How might this impact on clinical practice?

- JAK inhibitors are a relatively new therapeutic category and physicians may be looking at characteristics that predict response to therapy.
- No predictive features were identified for baricitinib treatment and when indicated, baricitinib can be prescribed to patients regardless of their clinical features.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterised by chronic inflammation of the synovial joints with resulting joint damage and destruction, decline in the quality of life and reduced life expectancy.[1] The emergence of therapies, such as small molecule inhibitors of components of the inflammatory pathways implicated in RA disease progression, have expanded the array of therapeutic options to treat the disease.

Janus kinase (JAK) inhibitors represent a relatively new therapeutic category for many clinicians and patients. As the accumulated literature on these drugs is relatively small compared with many biologic agents that have been used for over 15 years, there are legitimate questions regarding which kind of patients may respond best to these agents. There is also the need to identify

clinical characteristics that could be helpful in identifying patients who would be good candidates for a particular intervention.

Baricitinib is an oral selective JAK1/JAK2 inhibitor and has been approved in the European Union and several other countries for the treatment of moderately to severely active RA in adults.[2] Two phase III trials, RA-BEAM and RA-BUILD, assessed the efficacy of baricitinib in patients who had an inadequate response or intolerability to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and who had not been previously exposed to biologic DMARDs (bDMARDs).[3 4] The effects of patient characteristics at baseline such as age, previous use of csDMARDs, disease duration or rheumatoid factor (RF) and anticitrullinated peptide antibody (ACPA) status on the response to baricitinib treatment have not been previously assessed. The current subgroup analysis explore the extent to which baseline characteristics influence the response to baricitinib treatment.

METHODS

Study design

This post hoc analysis aimed to assess the effect of selected baseline characteristics and disease activity measures on the efficacy and safety of baricitinib at 12 weeks and structural progression at 24 weeks in patients from two randomised, double-blind, phase III studies. The RA-BEAM (NCT01710358) and RA-BUILD (NCT01721057) trials were designed by the sponsor, Eli Lilly and Company, an independent academic advisory board, and Incyte. The studies were conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines and were approved by the Quorum Review IRB #27 257 (RA-BEAM) and Quorum Review IRB #27 258 (RA-BUILD). Ethics approvals were also obtained for all 281 sites for the RA-BEAM trial and 182 sites for the RA-BUILD trial. All patients provided written informed consent. The full methodologies and the results of the trials have been reported previously by Taylor *et al*[3] and Dougados *et al*.[4] Briefly, the primary end point for these studies was the proportion of patients that achieved American College of Rheumatology 20% improvement (ACR20) response at week 12.[5] Several secondary and exploratory objectives including change from baseline to week 12 in Health Assessment Questionnaire-Disability Index (HAQ-DI) and Disease Activity Score for 28 joints based on high-sensitivity C reactive protein levels (DAS28-hsCRP), proportion of patients achieving Simplified Disease Activity Index (SDAI) ≤3.3 and change from baseline to week 24 in joint damage measured by modified Total Sharp Score (mTSS) were also evaluated in both trials.[6–9]

Patient population

Patients in both trials were ≥18 years of age with active RA as defined by the ACR and the European League Against Rheumatism 2010 criteria for classification of RA.[10] Eligible patients had either an inadequate response to or were intolerant to one or more csDMARDs. Patients were excluded if they received previous treatment with bDMARDs or recently experienced serious infections. RA-BEAM was a 52-week study in which patients were randomised in a 3:3:2 ratio to placebo, once-daily baricitinib 4 mg or adalimumab 40 mg biweekly. RA-BUILD was a 24-week study in which patients were randomly assigned in a 1:1:1 ratio to either placebo or baricitinib at a 2 or 4 mg dose once daily. Randomisation was stratified by geographical location and the status of joint erosion determined at baseline. All patients continued their background csDMARD use throughout the studies.

Subgroup analysis

Integrated patient populations were generated from the two studies to combine data from the placebo and baricitinib 4 mg treatment arms from each study. Since only the RA-BUILD trial assessed the baricitinib 2 mg dose, we did not examine the response in this patient group for the combined analysis. The current subgroup analyses were performed post hoc on the combined groups to determine whether variations in select baseline characteristics had an effect on the efficacy and safety of baricitinib treatment. Subgroups analysed included baseline demographic characteristics such as age (<65 or ≥65 years), gender, ethnicity, tobacco use, weight, body mass index (greater or less than the median), disease duration and number of csDMARDs used previously. Disease-related clinical characteristics that were assessed included seropositivity (RF and ACPA negative or RF/ACPA positive), DAS28-hsCRP high disease activity (>5.1) and moderate/low disease activity (≤5.1) categories, as well as SDAI and HAQ-DI score tertiles.

Efficacy outcomes in the selected subgroups were evaluated at week 12, the primary time point in the trials, by the proportion of patients achieving an ACR20 response, low disease activity as defined by the SDAI ≤11 score, and change from baseline in DAS28-hsCRP compared with placebo. Other categorical outcomes that were evaluated included the ACR50 and ACR70 response rates.

Smoking is a well-established risk factor for the development of RA[11] and obesity has been implicated in the poor response to treatment among patients with RA.[12] Since these two factors have been shown to influence joint damage in patients with RA, radiographic progression of joint damage in the hands and feet from baseline to week 24 was assessed using the van der Heijde mTSS, and compared between placebo and baricitinib 4 mg treated patients based on their smoking status and their weight subgroup at baseline.

Safety events were captured on all randomised patients in the age subgroup who received ≥1 dose of the study drug with postbaseline observation. Adverse events (AEs) were reported in preselected categories such as serious adverse events (SAEs), discontinuation from study and death.

Statistical analysis

In the current post hoc analysis, the integrated data from both the trials provided samples for placebo (N=716) and for baricitinib 4 mg (N=714) treated patients. Patient demographics, baseline disease characteristics and safety results were compiled using summary statistics including sample size and percentages by treatment group.

For the subgroup analysis, comparisons between each baricitinib 4 mg and placebo group were performed across subgroups at 12 weeks on the modified intent-to-treat population, which was defined as all randomised patients who received ≥1 dose of the study drug. For the categorical measurements, non-responder imputation was used in the analysis of patients who received either rescue therapy or discontinued from the study or study treatment. Consistency of baricitinib treatment effect across the subgroups and the interaction between treatment and subgroups was evaluated using logistic regression model with the factors treatment group, subgroup, treatment-by-subgroup and study included in the model. When the logistic regression sample size requirements were not met (<5 responders in any of the factors in the model), interaction P value was not assessed.

An interaction P value ≤0.10 was considered to be statistically significant assuming that there is less power to detect interaction effect than the main effect association in the model for a given sample size. Within a subgroup, odds ratio (OR) and 95% confidence interval (CI) were calculated from a logistic regression model with treatment group and study as factors. When the logistic regression sample size requirements were not met (<5 responders in any study or treatment), the Cochran-Mantel-Haenszel test stratified by study was applied to generate P values and ORs. Interpretation of subgroup interaction analyses that had a P value of ≤0.10 began with an examination of the direction (same as or opposite to overall treatment effect) and then the magnitude of the treatment effect across the strata.

For the continuous outcomes, DAS28-hsCRP (change from baseline to week 12) and mTSS (change from baseline to week 24), analysis of covariance (ANCOVA) model was used to evaluate interaction P values with factors baseline, treatment group, subgroup, study, and treatment-by-subgroup included in the model. For least squares mean (LSM) change from baseline, ANCOVA model was used with the factors baseline, treatment groups and study included in the model. Modified last observation carried forward imputation was applied for missing data in the continuous measurements.

RESULTS

Patient characteristics

The baseline demographics and disease characteristics were similar between the placebo and baricitinib 4 mg study groups. Patients in the subgroup analysis were predominantly <65 years of age (~83%), female (~79%) and white (~64%), with a majority in the ≥60 to <100 kg weight category (~63%). A substantial proportion of patients (72%) had a high baseline disease activity (DAS28-hsCRP>5.1), while 90% of patients were positive for either RF or ACPA. Detailed patient demographic and disease characteristics are listed in table 1.

Primary results

Patients in both studies achieved the primary analysis end points, with significantly more patients in the baricitinib 4 mg treatment arm achieving an ACR20 response at week 12 than patients in the placebo arm.[3 4] Several secondary end points, such as improvements in DAS28-hsCRP, SDAI remission rate (≤3.3), and HAQ-DI scores, were also achieved at week 12 in baricitinib-treated patients compared with placebo-treated patients in both studies.[3 4]

In the current subgroup analysis, the proportion of patients achieving ACR20 response, the primary clinical efficacy outcome, was significantly higher in the baricitinib 4 mg group compared with the placebo group in all of the selected subgroups assessed at 12 weeks (figure 1). Patient demographics had no apparent effect on the efficacy of baricitinib therapy. No significant interaction P values (≤0.10) were noted for majority of the subgroups. However, quantitative differences were observed in some smaller subgroups of patients; those in the non-Asian/non-white ethnic group, those ≥100 kg in the weight category and patients who tested negative for RF and ACPA at baseline (interaction P values of subgroups—0.125, 0.058 and 0.050, respectively). The small number of patients in these groups (<100) resulted in wide CIs and may have contributed to these observations.

The ACR50 and ACR70 response rates showed a similar trend favouring baricitinib 4 mg treatment over placebo in the baseline characteristics and disease categories tested (see online supplementary figures 1 and 2). Efficacy, as measured by the proportion of patients achieving low disease activity (SDAI ≤11) at week 12, was also observed consistently in the baricitinib-treated group with numerically higher response rates observed in the baricitinib 4 mg treated patients compared with placebo-treated patients. Improvement from baseline to week 12 in DAS28-hsCRP score was observed in baricitinib 4 mg treated patients over placebo-treated patients in all the baseline and clinical characteristics subgroups analysed (table 2). Interaction P values were not significant for majority of the subgroups evaluated.

Patient demographics, such as age, gender and length of time since RA diagnosis, had no apparent effect on baricitinib efficacy. Quantitative differences were observed in some subgroups; patients in the non-Asian/non-white ethnic group, those ≥100 kg in the weight category, and those who were RF and ACPA negative at baseline. At least one strata in these subgroups was relatively small (<100 patients).

The effects of individual variables in this analysis can be visualised in the forest plot in figure 1. CIs overlapped unity (1.0) on three domains: ethnicity other,

Table 1 Baseline patient demographics and disease characteristics

	Placebo (N=716) n (%)	Baricitinib 4 mg (N=714) n (%)
Age group (years)		
<65	603 (84.2)	578 (81.0)
≥65	113 (15.8)	136 (19.0)
Gender		
Female	571 (79.7)	562 (78.7)
Male	145 (20.3)	152 (21.3)
Race		
Asian	208 (29.1)	202 (28.3)
White	455 (63.6)	460 (64.4)
Other	52 (7.3)	51 (7.1)
Weight (kg)		
<60	219 (30.6)	191 (26.8)
≥60 to <100	436 (60.9)	461 (64.6)
≥ 100	61 (8.5)	62 (8.7)
BMI		
≤Median	368 (51.4)	345 (48.3)
>Median	348 (48.6)	368 (51.5)
Tobacco use		
Smoker	139 (19.4)	151 (21.2)
Non-smoker	577 (80.6)	562 (78.8)
Time from RA diagnosis (years)		
<1	106 (14.8)	114 (16.0)
≥1 and <5	234 (32.7)	233 (32.6)
≥5 and <10	166 (23.2)	166 (23.3)
≥10	210 (29.3)	201 (28.2)
Serology		
RF and ACPA (–)	70 (9.8)	71 (9.9)
RF or ACPA (+)	646 (90.2)	643 (90.1)
Previous csDMARD use		
≤1	302 (42.2)	342 (47.9)
=2	250 (34.9)	206 (28.9)
≥3	164 (22.9)	166 (23.2)
DAS28-hsCRP score		
≤5.1	210 (29.3)	182 (25.5)
>5.1	502 (70.1)	530 (74.2)
SDAI		
Lowest tertile	242 (33.8)	223 (31.2)
Middle tertile	240 (33.5)	246 (34.5)
Highest tertile	225 (31.4)	235 (32.9)
HAQ-DI		
Lowest tertile	250 (34.9)	256 (35.9)
Middle tertile	262 (36.6)	238 (33.3)
Highest tertile	200 (27.9)	218 (30.5)

ACPA, anticitrullinated peptide antibody; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-hsCRP, Disease Activity Score for 28 joint counts based on the level of high-sensitivity C reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index; N, number of modified intent-to-treat patients in the specified treatment population; n, number of patients in specified category; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index.

weight ≥100 kg and RF and ACPA (–), at the time of the primary end point, introducing the possibility of non-significant efficacy differences although type II error cannot be ruled out due to the small sample sizes within these subgroups and lack of control for multiplicity. In a population pharmacokinetic analysis of baricitinib in patients with RA, only changes in body weight had a statistically significant effect on the apparent volume of distribution and on renal clearance, but the size of the effect was small and was not considered to be clinically relevant.[13] Patients higher in weight also exhibited higher levels of disease activity at baseline.

Radiographic progression at week 24 (least squares mean (LSM) change in mTSS from baseline using linear extrapolation for missing data) between placebo-treated and baricitinib-treated patients was also assessed in the smoker/non-smoker and weight subgroups (table 3). There was no statistically significant interaction observed between treatment and smoking status (interaction P value=0.942). Smokers and non-smokers, respectively, had LSM change from baseline of 0.59 and 0.24 in the baricitinib 4 mg group and 1.06 and 0.72 in the placebo group. When compared with placebo-treated patients in the same subgroup, similar magnitudes of improvement were observed—LSM difference −0.47 and −0.48 for smoker and non-smoker subgroups, respectively. Regardless of treatment, lower rates of joint damage progression were observed among patients with increasing weight. However, no statistically significant interaction was observed for treatment by weight (interaction P value=0.566). In all weight subgroups analysed, less radiographic progression was observed in baricitinib 4 mg treated patients compared with the placebo-treated patients within the same subgroup.

Safety results

An evaluation of safety events from weeks 0 to 12 in the age subgroup, <65 and ≥65 years, showed similar number of AEs between placebo and baricitinib 4 mg groups; ~87% in the <65 age category and ~97% in the ≥65 age category (table 4). Similar number of SAEs were reported across treatment groups in both age subgroups (15 placebo-treated and 10 baricitinib 4 mg

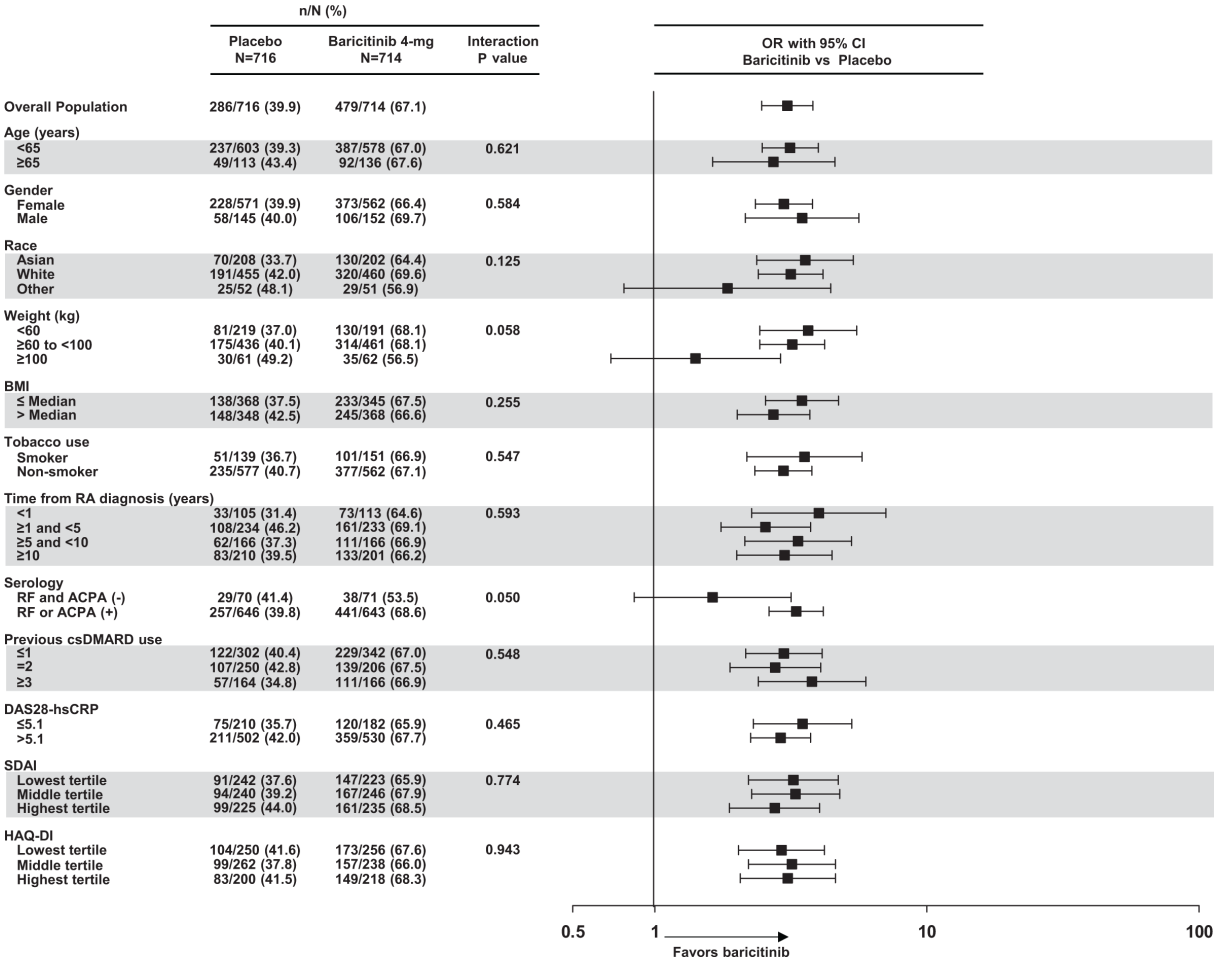

Figure 1 Percentage of patients achieving 20% improvement in the American College of Rheumatology criteria at week 12 by patient demographic and disease characteristics subgroups. Data (non-responder imputation) are presented as n/N (%) patients. ACPA, anticitrullinated peptide antibody; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-hsCRP, Disease Activity Score for 28 joint counts based on the level of high-sensitivity C reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index; N, number of modified intent-to-treat patients in the specified treatment population; n, number of patients in specified category; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index.

treated patients in <65 age group; 7 placebo-treated and 6 baricitinib 4 mg treated patients in ≥65 age group). The number of patients discontinuing from study due to AEs in the baricitinib 4 mg group were not different from the placebo group.

DISCUSSION

The number of new therapies to treat RA, as well as the strategies developed to employ them, have expanded immensely over the past three decades. Despite this, clinicians face the challenge of identifying whether individual patients are more or less likely to respond to the next therapeutic option. As the therapeutic decision processes move towards personalised treatment for individual patients, the use of subgroup analysis across pooled studies takes on increasing importance as a tool to identify factors that might enable greater precision. With newer targeted therapies, such as JAK inhibitors, it has also become essential to establish the efficacy and safety of the treatments in the various populations of patients with RA, taking into consideration their baseline disease characteristics and previous treatments.[14]

This post hoc analysis of two pooled phase III studies was performed in over 1400 patients with active RA and an inadequate response to csDMARDs. On a group-wise basis, baricitinib demonstrated meaningful benefit in this RA population.[3 4] However, to better understand the potential utility of baricitinib for an individual patient in a clinical setting, population subgroup analyses were performed across a variety of patient demographic, clinical characteristic and prior drug exposure domains.

The quantitative differences observed in patients who were non-Asian/non-white, those ≥100 kg and those who were RF and ACPA negative at baseline should be evaluated with caution. The small number of non-Asian/non-white patients results in wide CIs with the point estimate favouring baricitinib. Published literature indicates

Table 2 Change from baseline in DAS28-hsCRP and proportion of patients achieving SDAI≤11 at week 12

	DAS28-hsCRP Change from baseline LSM (SE)			Patients achieving SDAI≤11 n/N-obs (%)		
	Placebo (N=716)	Baricitinib 4 mg (N=714)	Interaction P value	Placebo (N=716)	Baricitinib 4 mg (N=714)	Interaction P value
Age group (years)						
<65	−1.0 (0.05)	−2.1 (0.05)	0.561	102/603 (16.9)	221/578 (38.2)	0.407
≥65	−1.2 (0.11)	−2.4 (0.10)		20/113 (17.7)	63/136 (46.3)	
Gender						
Female	−1.1 (0.05)	−2.2 (0.05)	0.290	97/571 (17.0)	226/562 (40.2)	0.735
Male	−1.1 (0.10)	−2.3 (0.10)		25/145 (17.2)	58/152 (38.2)	
Race						
Asian	−0.9 (0.08)	−2.2 (0.08)	0.030	29/208 (13.9)	82/202 (40.6)	0.029
White	−1.1 (0.06)	−2.2 (0.06)		78/455 (17.1)	186/460 (40.4)	
Other	−1.3 (0.19)	−2.0 (0.19)		15/52 (28.8)	16/51 (31.4)	
Weight (kg)						
<60	−1.1 (0.08)	−2.3 (0.09)	0.022	35/219 (16.0)	80/191 (41.9)	0.064
≥60 to <100	−1.0 (0.06)	−2.2 (0.06)		73/436 (16.7)	187/461 (40.6)	
≥100	−1.3 (0.15)	−1.9 (0.15)		14/61 (23.0)	17/62 (27.4)	
BMI						
≤Median	−1.0 (0.06)	−2.3 (0.06)	0.001	58/368 (15.8)	148/345 (42.9)	0.077
>Median	−1.2 (0.07)	−2.1 (0.06)		64/348 (18.4)	135/368 (36.7)	
Tobacco use						
Smoker	−0.9 (0.10)	−2.3 (0.10)	0.136	21/139 (15.1)	65/151 (43.0)	0.269
Non-smoker	−1.1 (0.05)	−2.2 (0.05)		101/577 (17.5)	218/562 (38.8)	
Time from RA diagnosis (years)						
< 1	−0.9 (0.11)	−2.0 (0.11)	0.488	12/105 (11.4)	31/113 (27.4)	0.560
≥1 and < 5	−1.1 (0.08)	−2.2 (0.08)		46/234 (19.7)	97/233 (41.6)	
≥ 5 and < 10	−1.0 (0.10)	−2.3 (0.09)		28/166 (16.9)	79/166 (47.6)	
≥ 10	−1.1 (0.09)	−2.2 (0.09)		36/210 (17.1)	77/201 (38.3)	
Serology						
RF and ACPA (-)	−1.1 (0.15)	−1.8 (0.15)	0.010	13/70 (18.6)	17/71 (23.9)	0.033
RF or ACPA (+)	−1.1 (0.05)	−2.2 (0.05)		109/646 (16.9)	267/643 (41.5)	
Previous csDMARD use						
≤1	−1.1 (0.07)	−2.2 (0.07)	0.443	56/302 (18.5)	139/342 (40.6)	0.653
=2	−1.1 (0.08)	−2.2 (0.08)		47/250 (18.8)	87/206 (42.2)	
≥3	−0.9 (0.09)	−2.2 (0.09)		19/164 (11.6)	58/166 (34.9)	
DAS28-hsCRP score						
≤ 5.1	−0.7 (0.07)	−1.7 (0.07)	0.511	58/210 (27.6)	105/182 (57.7)	0.941
> 5.1	−1.2 (0.06)	−2.4 (0.06)		63/502 (12.5)	177/530 (33.4)	
SDAI						
Lowest tertile	−0.8 (0.06)	−1.8 (0.07)	0.539	68/242 (28.1)	129/223 (57.8)	0.925
Middle tertile	−1.0 (0.08)	−2.2 (0.08)		33/240 (13.8)	92/246 (37.4)	
Highest tertile	−1.3 (0.09)	−2.6 (0.09)		20/225 (8.9)	57/235 (24.3)	
HAQ-DI						

Continued

Table 2 Continued

	DAS28-hsCRP Change from baseline LSM (SE)			Patients achieving SDAI≤11 n/N-obs (%)		
	Placebo (N=716)	Baricitinib 4 mg (N=714)	Interaction P value	Placebo (N=716)	Baricitinib 4 mg (N=714)	Interaction P value
Lowest tertile	−1.0 (0.07)	−2.1 (0.07)	0.489	64/250 (25.6)	130/256 (50.8)	0.612
Middle tertile	−1.0 (0.07)	−2.2 (0.08)		32/262 (12.2)	85/238 (35.7)	
Highest tertile	−1.2 (0.09)	−2.3 (0.09)		25/200 (12.5)	67/218 (30.7)	

ACPA, anticitrullinated peptide antibody; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-hsCRP, Disease Activity Score for 28 joint counts based on the level of high-sensitivity C reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index; LSM, least squares mean; N, number of modified intent-to-treat patients in the specified treatment population; n, number of patients in specified category; N-obs, number of patients in the analysis; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index.

Table 3 Change from baseline in mTSS at week 24[a] in select subgroups

	Patients with mTSS results N		Change from baseline to week 24 LSM (SE)		Interaction P value
	Placebo	Baricitinib 4 mg	Placebo	Baricitinib 4 mg	
Tobacco use					
Smoker	126	142	1.06 (0.26)	0.59 (0.25)	0.942
Non-smoker	518	525	0.72 (0.08)	0.24 (0.08)	
Weight (kg)					
<60	200	180	1.11 (0.17)	0.45 (0.18)	0.566
≥60 to <100	391	432	0.67 (0.11)	0.27 (0.10)	
≥100	53	56	0.43 (0.14)	0.10 (0.14)	

[a]Data included up to rescue using linear extrapolation.
LSM, least squares mean; mTSS, modified Total Sharp Score; N, number of modified intent-to-treat patients in the specified treatment subgroup.

Table 4 Safety events in age subgroup from weeks 0 to 12

	Placebo			Baricitinib 4 mg		
	Total (N=716)	<65 years (N=603)	≥65 years (N=113)	Total (N=714)	<65 years (N=578)	≥65 years (N=136)
≥1 Adverse events	633	524 (86.9)	109 (96.5)	636	503 (87.0)	133 (97.8)
SAE[a]	22	15 (2.5)	7 (6.2)	16	10 (1.7)	6 (4.4)
Cardiac disorders	3	2 (0.3)	1 (0.9)	1	1 (0.2)	0
Serious infections	8	6 (1.0)	2 (1.8)	6	3 (0.5)	3 (2.2)
Zoster	0	0	0	2	0	2 (1.5)
Tuberculosis	0	0	0	0	0	0
Malignancies	1	0	1 (0.9)	1	1 (0.2)	0
Discontinuation from study	21	15 (2.5)	6 (5.3)	20	13 (2.2)	7 (5.1)
Death	2	2 (0.3)	0	0	0	0

Data presented as n (%).
N, number of patients in the specified treatment subgroup; n, number of patients in the specified category
[a]SAE, serious adverse event, reported on the basis of conventional International Conference on Harmonisation definitions.

that patients with RA who are seropositive for autoantibodies respond better to rituximab than those who are seronegative[15–19]; and bDMARD-naïve patients who are seropositive respond better to abatacept than those who are seronegative.[20 21] However, as noted earlier, comparatively few patients were seronegative in the current

analysis and the small patient population in this category limits confidence in efficacy comparisons between the seropositive and seronegative subgroups. Interestingly, the response to baricitinib was similar across levels of disease duration and the number of prior csDMARDs used, suggesting that baricitinib is an equally effective treatment option for patients regardless of their previous treatment experience. Similarly, the other efficacy outcomes evaluated, improvement from baseline in DAS28-hsCRP score and proportion of patients achieving SDAI ≤11, favoured baricitinib 4 mg treatment over placebo with no significant interaction P values observed for majority of the subgroups.

We also evaluated two important factors affecting joint damage progression— tobacco use and obesity. Differences in smoking habit and weight did not affect the therapeutic benefit of baricitinib as baricitinib 4 mg treated patients showed less radiographic progression compared with the placebo-treated patients in the same subgroup.

Safety however may be an even more important variable when deciding which therapy to initiate. The number of AEs, SAEs and discontinuations due to AEs were greater in the ≥65 age group compared with patients in the <65 years age group (table 4). However, the numbers were similar in patients treated with baricitinib and placebo within each age group (table 4). Infections and serious infections occurred in similar proportions in each age group and was similar between placebo-treated and baricitinib-treated patients.

There are limitations to the type of analyses presented here. The timeframe for interpretation of safety data is focused to 12 weeks for symptoms, signs and safety. However, this does represent a reasonable time period to assess whether individual baseline parameters might influence either likelihood of efficacy or AE. The occurrence of AEs may certainly be delayed and extension studies are in progress to assess the long-term safety of baricitinib treatment. In this analysis, multiple categorical variables were evaluated, and some subgroups contained few patients, which limited the robustness of the comparisons. Multiple comparisons were not adjusted for, but it was noted that significant interaction P values were observed infrequently and inconsistently indicating minimal treatment heterogeneity across subgroups. Additionally, since only one of the studies included in this post hoc analysis assessed two doses of baricitinib, the effect of dose was not examined in this report.[4]

In conclusion, baricitinib 4 mg demonstrated a beneficial treatment effect over placebo in this post hoc analysis of bDMARD-naïve patients with RA who were csDMARD inadequate responders. This positive clinical response was observed in patients across the range of baseline characteristics in multiple efficacy outcomes measured, and with a safety profile consistent with that previously described and not related to baseline characteristics.

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