Efficacy and safety data based on historical or pre-existing conditions at baseline for patients with active rheumatoid arthritis who were treated with baricitinib

Patients with rheumatoid arthritis (RA) have a high prevalence of comorbidities.[1] This post-hoc analysis investigated the effect of select comorbidities (depression, osteoporosis, hepatic, cardiovascular or pulmonary disorders) on the efficacy and safety of baricitinib 4 mg once daily in patients with moderate-to-severe active RA and an inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).

Data from the placebo-controlled periods of five baricitinib studies[2–6] were pooled for baricitinib 4 mg; data for baricitinib 2 mg were not analysed due to low (n=302) patient numbers. Additional data for all baricitinib-treated patients with a median exposure of 2 years were derived from an ongoing open-label, long-term extension (LTE) study that included patients from phase II and III studies (RA-BEYOND; NCT01885078).[7] Efficacy outcomes were evaluated at week 12 (vs placebo). Interaction of comorbidity-by-treatment was analysed using logistic regression or analysis of covariance. Safety observations up to week 16 (vs placebo) and during the LTE were summarised by the Medical Dictionary for Regulatory Activities preferred term.

Data from 1684 patients (803, baricitinib 4 mg; 881, placebo) from the placebo-controlled periods were analysed. The mean (SD) age was 52.7 (12.1) years, with only 38 (2.3%) patients aged ≥75 years; most patients (1506, 89.4%) were receiving background methotrexate, alone or in combination with another csDMARD. The numbers of patients receiving placebo and baricitinib 4 mg combined (with or without each comorbidity, respectively) were 133/1551 for depression, 247/1437 for osteoporosis, 424/1260 for hepatic disorders, 731/953 for cardiovascular disorders, and 166/1518 for pulmonary disorders. Demographic and clinical characteristics within each comorbidity subgroup were similar between patients randomised to baricitinib or placebo.

Higher proportions of patients achieved all clinical endpoints with baricitinib 4 mg than with placebo at week 12 across subgroups (table 1). Response rates in patients with or without each comorbidity who received baricitinib were generally close to overall response rates, with the exception of depression, where numerically lower response rates were observed in patients with versus without depression and overall (table 1). Responses to baricitinib versus placebo were similar between patients with or without comorbidity within each comorbidity subgroup, even for those with/without depression (p>0.1).

The safety analysis set from the placebo-controlled periods included 1683 patients (802, baricitinib; 881, placebo) with 235.2 and 246.9 patient-years of exposure (PYE) to baricitinib 4 mg or placebo, respectively. Similar proportions of patients experienced ≥1 treatment-emergent adverse events (TEAEs) between baricitinib and placebo across comorbidity subgroups (table 1). The most common TEAEs for the overall population were nasopharyngitis (5.6%, baricitinib vs 5.2%, placebo), upper respiratory tract infections (4.5% vs 3.5%), urinary tract infections (3.5% vs 2.6%) and bronchitis (2.9% vs 2.6%). Serious adverse events (SAEs) and discontinuations were infrequent, occurring at similar rates across subgroups for baricitinib and placebo. SAE and discontinuation rates for baricitinib-treated patients with/without each comorbidity were generally close to overall rates, although numerical differences were observed between patients with depression (lower rates), osteoporosis (higher rates) or pulmonary disorders (higher rates) and those without these comorbidities.

In the LTE study, safety data were available from 3439 patients with a total of 6633 PYE to baricitinib. Overall, the incidence of TEAEs, SAEs, discontinuations and reported deaths was similar between patients with or without comorbidity within each comorbidity subgroup (table 1). Further, the exposure-adjusted incidence rates for all patients were lower in the LTE than during the placebo-controlled period for all safety outcomes assessed. The numerical differences between patients with/without each comorbidity observed after 16 weeks (see above) were not observed in the LTE study.

This is the first analysis assessing the impact of select comorbidities on the efficacy and safety of baricitinib 4 mg. Limitations of this post-hoc analysis include the analysis of patient data derived from randomised clinical trials rather than real-world patient data, such that patients with certain acute or historical conditions, unstable illness, or certain laboratory abnormalities were excluded from the trials (see online supplementary text); the limited number of patients in each comorbidity subgroup and the limited duration of analyses; the non-inclusion of all known comorbidities in RA; the mix of comorbidities included in each subgroup, which could vary in severity and overall impact on patients; the inability to assess adverse events of specific interest and whether comorbidity severity improved or worsened following baricitinib treatment; and the inability to conclude on the efficacy and safety of baricitinib in patients aged ≥75 years and/or exposed to baricitinib 2 mg due to low patient numbers. Planned analyses of safety data from registries or healthcare databases in the USA and Europe are expected to address many of the current limitations.

Baricitinib 4 mg showed similar efficacy and safety during placebo-controlled and LTE observation periods regardless of the presence or absence of select comorbidities in patients with moderate-to-severe active RA and an inadequate response to csDMARDs. No trends for increased risk of safety events related to comorbidity were observed across comorbidity subgroups for baricitinib during a median exposure of 2 years. Further studies are needed to confirm the data presented, which provide a hypothesis only.

Trial registration numbers: NCT01185353, NCT01469013, NCT00902486, NCT01710358 and NCT01721057.

Table 1 Efficacy and safety data reported by select comorbidities in patients treated with baricitinib or placebo*

	Depression	No depression	Osteoporosis	No osteoporosis	Hepatic disorders	No hepatic disorders	CV disorders	No CV disorders	Pulmonary disorders	No pulmonary disorders	Overall
Baricitinib 4 mg											
Efficacy outcomes at week 12											
Patients, N	64	739	113	690	222	581	350	453	77	726	803
ACR20 response (%)†	59.4	68.2	65.5	67.8	67.1	67.6	68.3	66.9	66.2	67.6	67.5
ACR50 response (%)†	34.4	41.7	40.7	41.2	40.5	41.3	40.9	41.3	40.3	41.2	41.1
DAS 28-hsCRP ≤3.2 response (%)†	31.3	44.9	46.9	43.3	42.8	44.2	44.9	43.0	37.7	44.5	43.8
Change in HAQ-DI‡	−0.46	−0.54	−0.36	−0.55	−0.58	−0.53	−0.54	−0.52	−0.51	−0.53	−0.53
Safety outcomes at week 16											
Patients, N	64	738	113	689	222	580	350	452	77	725	802
Any TEAE, n (%), (EAIR)	45 (70.3), (246)	450 (61.0), (208)	70 (61.9), (216)	425 (61.7), (210)	152 (68.5), (232)	343 (59.1), (202)	227 (64.9), (221)	268 (59.3), (202)	62 (80.5), (284)	433 (59.7), (203)	495 (61.7), (210)
SAE, n (%), (EAIR)	0, (0.0)	25 (3.4), (11.5)	9 (8.0), (27.8)	16 (2.3), (7.9)	8 (3.6), (12.2)	17 (2.9), (10.0)	14 (4.0), (13.6)	11 (2.4), (8.3)	4 (5.2), (18.3)	21 (2.9), (9.8)	25 (3.1), (10.6)
Discontinuation due to AEs, n (%), (EAIR)	1 (1.6), (5.5)	24 (3.3), (11.1)	7 (6.2), (21.6)	18 (2.6), (8.9)	9 (4.1), (13.7)	16 (2.8), (9.4)	14 (4.0), (13.6)	11 (2.4), (8.3)	3 (3.9), (13.8)	22 (3.0), (10.3)	25 (3.1), (10.6)
Deaths, n (%), (EAIR)	0, (0.0)	0, (0.0)	0, (0.0)	0, (0.0)	0, (0.0)	0, (0.0)	0, (0.0)	0, (0.0)	0, (0.0)	0, (0.0)	0, (0.0)
Placebo											
Patients, N	69	812	134	747	202	679	381	500	89	792	881
Efficacy outcomes at week 12											
ACR20 response (%)†	31.9	39.8	32.1	40.4	37.1	39.8	40.7	38.0	32.6	39.9	39.2
ACR50 response (%)†	8.7	14.9	11.9	14.9	11.4	15.3	14.4	14.4	12.4	14.6	14.4
DAS 28-hsCRP ≤3.2 response (%)†	13.0	16.9	12.7	17.3	12.9	17.7	15.7	17.2	16.9	16.5	16.6
Change in HAQ-DI§	−0.20	−0.26	−0.08	−0.27	−0.28	−0.26	−0.27	−0.23	−0.17	−0.26	−0.25
Safety outcomes at week 16											
Any TEAE, n (%), (EAIR)	57 (82.6), (301)	437 (53.8), (192)	91 (67.9), (251)	403 (53.9), (191)	119 (58.9), (207)	375 (55.2), (198)	228 (59.8), (212)	266 (53.2), (191)	59 (66.3), (238)	435 (54.9), (196)	494 (56.1), (200)
SAE, n (%), (EAIR)	6 (8.7), (31.7)	25 (3.1), (11.0)	9 (6.7), (24.9)	22 (2.9), (10.4)	5 (2.5), (8.7)	26 (3.8), (13.7)	16 (4.2), (14.9)	15 (3.0), (10.8)	2 (2.2), (8.1)	29 (3.7), (13.1)	31 (3.5), (12.6)
Discontinuation due to AEs, n (%), (EAIR)	3 (4.3), (15.9)	21 (2.6), (9.2)	9 (6.7), (24.9)	15 (2.0), (7.1)	6 (3.0), (10.4)	18 (2.7), (9.5)	12 (3.1), (11.1)	12 (2.4), (8.6)	4 (4.5), (16.1)	20 (2.5), (9.0)	24 (2.7), (9.7)
Deaths, n (%), (EAIR)	1 (1.4), (5.3)	0, (0.0)	1 (0.7), (2.8)	0, (0.0)	0, (0.0)	1 (0.1), (0.5)	1 (0.3), (0.9)	0, (0.0)	0, (0.0)	1 (0.1), (0.5)	1 (0.1)§, (0.4)
Baricitinib safety outcomes after median exposure of 2 years											
Patients, N	342	3097	500	2939	810	2629	1535	1904	373	3066	3439
Any TEAE, n (%), (EAIR)	318 (93.0), (51.4)	2592 (83.7), (43.1)	444 (88.8), (45.9)	2466 (83.9), (43.5)	711 (87.8), (45.1)	2199 (83.6), (43.5)	1351 (88.0), (44.8)	1559 (81.9), (43.1)	343 (92.0), (45.7)	2567 (83.7), (43.6)	2910 (84.6), (43.9)
SAE, n (%), (EAIR)	73 (21.3), (11.8)	489 (15.8), (8.1)	132 (26.4), (13.7)	430 (14.6), (7.6)	168 (20.7), (10.7)	394 (15.0), (7.8)	348 (22.7), (11.5)	214 (11.2), (5.9)	102 (27.3), (13.6)	460 (15.0), (7.8)	562 (16.3), (8.5)

Continued

Table 1 Continued

	Depression	No depression	Osteoporosis	No osteoporosis	Hepatic disorders	No hepatic disorders	CV disorders	No CV disorders	Pulmonary disorders	No pulmonary disorders	Overall
Discontinuation due to AEs, n (%), (EAIR)	36 (10.5), (5.8)	283 (9.1), (4.7)	71 (14.2), (7.3)	248 (8.4), (4.4)	93 (11.5), (5.9)	226 (8.6), (4.5)	173 (11.3), (5.7)	146 (7.7), (4.0)	35 (9.4), (4.7)	284 (9.3), (4.8)	319 (9.3), (4.8)
Deaths, n (%), (EAIR)	3 (0.9), (0.5)	10 (0.3), (0.2)	7 (1.4), (0.7)	6 (0.2), (0.1)	1 (0.1), (0.1)	12 (0.5), (0.2)	9 (0.6), (0.3)	4 (0.2), (0.1)	4 (1.0), (0.5)	9 (0.3), (0.2)	13 (0.4), (0.2)

Comorbidities and associated terms are based on the Medical Dictionary for Regulatory Activities classification system. Terms for depression included depressed mood, depression postoperative, depression, depressive symptoms, dysthymic disorder, major depression, suicidal ideation and suicide attempt. Terms for osteoporosis included low bone density (bone density decreased), non-traumatic bone fracture (osteoporotic fracture), osteopaenia, osteoporosis postmenopausal, osteoporosis and senile osteoporosis. Terms for hepatic disorders included alanine aminotransferase increased, aspartate aminotransferase increased, biliary cirrhosis primary, blood alkaline phosphatase increased, cholestasis, chronic hepatitis, drug-induced liver injury, gamma-glutamyltransferase increased, hepatic enzyme abnormal, hepatic enzyme increased, hepatic function abnormal, hepatic lesion, hepatic steatosis, hepatitis, hepatitis acute, hepatitis toxic, hepatomegaly, hypertransaminasaemia, hypoalbuminaemia, jaundice, liver disorder, liver function test abnormal, liver injury, liver operation, non-alcoholic steatohepatitis, serum hepatitis B virus core antibody positive, serum hepatitis B virus surface antibody positive, spider nevus, transaminases increased and varices oesophageal. Terms for cardiovascular disorders included acute myocardial infarction, blood cholesterol increased, blood glucose abnormal, blood glucose increased, cerebral infarction, cerebrovascular accident, coronary artery bypass, diabetes mellitus, diabetes mellitus inadequate control, diabetic ketoacidosis, essential hypertension, gestational diabetes, glucose tolerance impaired, hypercholesterolaemia, hyperglycaemia, hyperlipidaemia, hypertension, hypertensive cardiomyopathy, hypertensive heart disease, intermittent claudication, ischaemic stroke, labile hypertension, lacunar infarction, low-density lipoprotein increased, myocardial infarction, peripheral arterial occlusive disease, peripheral artery stenosis, subarachnoid haemorrhage, subdural haematoma, systolic hypertension and transient ischaemic attack. Terms for pulmonary disorders included allergic bronchitis, apnoea, asbestosis, aspirin-exacerbated respiratory disease, asthma, asthma exercise-induced, atelectasis, bronchial hyper-reactivity, bronchiectasis, bronchiolitis, bronchitis chronic, bronchospasm, bullous lung disease, chronic obstructive pulmonary disease, cor pulmonale chronic, diffuse panbronchiolitis, dyspnoea, dyspnoea exertional, emphysema, idiopathic pulmonary disease, infantile asthma, interstitial lung disease, Langerhans cell histiocytosis, lung consolidation, lung cyst, obstructive airways disorder, pneumoconiosis, pneumonitis, pulmonary bulla and pulmonary fibrosis. The number of patients with idiopathic pulmonary disease, interstitial lung disease or pulmonary fibrosis was low (6 and 8 patients for baricitinib 4 mg and placebo, respectively); thus, the impact of these conditions on baricitinib treatment outcomes cannot be concluded with certainty.

*Efficacy outcomes were assessed at week 12 for baricitinib and placebo; safety outcomes were recorded from baseline to week 16 for baricitinib and placeboin the randomised controlled trials and for all patients receiving baricitinib after a median exposure of 2 years in the long-term extension study.

†Percentage of patients achieving ACR20, ACR50 and DAS 28-hsCRP ≤3.2.

‡Least squares mean changes in HAQ-DI scores from baseline to week 12; negative changes indicate improvement from baseline.

§One death occurred in a patient receiving placebo; this patient had depression, osteoporosis and a cardiovascular disorder.

ACR, American College of Rheumatology; ACR20, 20% improvement from baseline in ACR criteria; ACR50, 50% improvement from baseline in ACR criteria; AE, adverse event; CV, cardiovascular; DAS28-hsCRP, Disease Activity Score for 28-joints based on the level of high-sensitivity C reactive protein; EAIR, exposure-adjusted incidence rate; HAQ-DI, Health Assessment Questionnaire–Disability Index; N, number of patients randomised and treated in each comorbidity subgroup; n, number of patients with event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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