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Baricitinib (rheumatoid arthritis) –

Addendum to Commission A17-14[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CDAI	Clinical Disease Activity Index
cDMARD	conventional disease-modifying antirheumatic drug
CI	confidence interval
DAS28-hsCRP	Disease Activity Score 28 high-sensitivity C-reactive protein
DMARD	disease-modifying antirheumatic drug
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HAQ-DI	Health Assessment Questionnaire-Disability Index
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
mITT	modified intention to treat
MTX	methotrexate
SAE	serious adverse event
SDAI	Simplified Disease Activity Index
SF-36v2	Short Form (36) – version 2 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 8 August 2017, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-14 (Baricitinib – Benefit assessment according to §35a Social Code Book V [1]).

In accordance with the G-BA's specification of the appropriate comparator therapy (ACT), benefit assessment A17-14 was structured in 4 research questions. For research questions 2 and 3, the company presented analyses of the JADV study and derived the added benefit for both research questions on the basis of the total population (referred to as "modified intention-to-treat [mITT] population" by the company) [2]. The subpopulations relevant for both research questions were only presented as additional information by the company. In benefit assessment A17-14 [1], the relevant subpopulation in accordance with the G-BA's specification of the ACT was used for each of the research questions 2 and 3 to derive the added benefit of baricitinib. The reasons for this approach were as follows: (1) The mITT population includes patients who, contrary to the recommendations provided in the European Public Assessment Report (EPAR) on baricitinib [3], were treated in the study with at least 1 further conventional disease-modifying antirheumatic drug (cDMARD) in addition to methotrexate (MTX). (2) Heterogeneity tests between the relevant subpopulations (which, correspondingly, in their totality only include part of the mITT population) allowed no assessment whether the mITT population can be used for the derivation of the added benefit for each of the research questions 2 and 3.

After the commenting procedure and the oral hearing, the G-BA commissioned IQWiG with the assessment of the total study population of the JADV study (hereinafter referred to as "mITT population").

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Assessment of the mITT population of the JADV study (research questions 2 and 3)

2.1.1 Research questions and study characteristics

Research questions 2 and 3 of the benefit assessment of baricitinib were the assessment of the added benefit of baricitinib in adult patients with moderate to severe active rheumatoid arthritis:

- with poor prognostic factors who have responded inadequately to prior treatment with 1 disease-modifying antirheumatic drug (conventional DMARDs, including MTX) (research question 2)
- who have responded inadequately to prior treatment with several disease-modifying antirheumatic drugs (conventional DMARDs, including MTX) (research question 3)

For these research questions, the company had presented the JADV study in its dossier. The JADV study was a randomized, multicentre, double-blind, parallel-group phase 3 study on the comparison of baricitinib + MTX with adalimumab + MTX. It included adult patients with moderate to severe active rheumatoid arthritis with inadequate response to MTX and no prior therapy with biologic DMARDs (bDMARDs). All patients had poor prognostic factors.

Hereinafter, in accordance with the G-BA's commission, the total population of the JADV study (mITT) is assessed below.

The description of the study and the characteristics of the interventions of the JADV study can be found in the benefit assessment [1]. The mITT population of the JADV study included n = 488 patients in the baricitinib + MTX arm and n = 330 patients in the adalimumab + MTX arm. 15.5% of these patients received at least 1 further cDMARD in addition to their concomitant treatment with MTX, which contradicts the EPAR recommendation on baricitinib and its approval [3,4].

Table 1 shows the characteristics of the patients of the mITT population in the JADV study.

Table 1: Characteristics of the study population – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (mITT population)

Study Characteristics Category	**Baricitinib + MTX**	**Adalimumab + MTX**
JADV	N[a] = 487	N[a] = 330
Age [years], mean (SD)	54 (12)	53 (12)
Sex [F/M], %	77/23	76/24
Region, n (%)		
Central and South America and Mexico	143 (29.4)	96 (29.1)
Eastern Europe	85 (17.5)	58 (17.6)
Japan	93 (19.1)	63 (19.1)
USA and Canada	40 (8.2)	26 (7.9)
Western Europe	29 (6.0)	20 (6.1)
Asia (without Japan)	48 (9.9)	33 (10.0)
Rest of the world	49 (10.1)	34 (10.3)
Disease duration: time between first diagnosis and randomization [years], mean (SD)	8.7 (8.6)	8.3 (7.9)
Functional status [HAQ-DI], mean (SD)	1.57 (0.68)	1.59 (0.70)
Tender joint count[b], mean (SD)	23.4 (13.0)	23.4 (13.7)
Swollen joint count[c], mean (SD)	15 (8.2)	15.4 (9.1)
Rheumatoid factor status, n (%)		
Positive	439 (90.1)	301 (91.2)
Negative	48 (9.9)	29 (8.8)
ACPA status, n (%)		
Positive	427 (87.7)	295 (89.4)
Negative	49 (10.1)	32 (32 (9.79)
Undetermined	11 (2.3)	3 (0.9)
DAS28-hsCRP, n (%)		
≤ 3.2	2 (0.4)	0 (0)
> 3.2 to ≤ 5.1	117 (24.1)	80 (24.3)
> 5.1	367 (75.5)	249 (75.7)
Renal function [eGFR], n (%)		
< 60 mL/min/1.73 m^2	19 (3.9)	16 (4.8)
≥ 60 mL/min/1.73 m^2	468 (96.1)	314 (95.2)
Bone/joint erosion score[d], mean (SD)	25.1 (28.3)	26.4 (28.7)
Joint space narrowing score[e] mean (SD)	17.3 (23.2)	18.0 (23.8)
Patients with adjustment of therapy[f], n (%)	43 (8.8)	51 (15.5)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	60 (12.3)[g]	44 (13.3)[g]

(continued)

Table 1: Characteristics of the study population – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (mITT population) (continued)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Based on 68 joints.
c: Based on 66 joints.
d: Based on the severity grade of erosion in 32 joints of the hands and 12 joints of the feet.
e: Based on the severity grade of joint space narrowing in 30 joints of the hands and 12 joints of both feet.
f: From week 16, patients with inadequate response received rescue therapy.
g: Institute's calculation.
ACPA: anti-citrullinated protein antibody; DAS: Disease Activity Score; eGFR: estimated glomerular filtration rate; F: female; HAQ-DI: Health Assessment Questionnaire-Disability Index; hsCRP: high-sensitivity C-reactive protein; M: male; MTX: methotrexate; n: number of patients in the category; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The risk of bias at study level for the JADV study was rated as low [1].

2.1.2 Results based on the mITT population

The choice of patient-relevant outcomes for the assessment based on the mITT population concurs with that of the benefit assessment [1]. The assessment was only supplemented with the outcomes for which no data were available in the benefit assessment for the relevant subpopulation.

Table 2 shows for which outcomes data for the mITT population were available in the JADV study. Table 3 shows the risk of bias for the relevant outcomes.

Table 2: Matrix of outcomes – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (mITT population)

Study	Outcomes															
	All-cause mortality	Remission (SDAI ≤ 3.3; CDAI ≤ 2.8; Boolean definition)	Low disease activity (DAS28-hsCRP ≤ 3.2; SDAI ≤ 11; CDAI ≤ 10)	Tender joint count[a]	Swollen joint count[a]	Pain (VAS)	Disease activity (VAS)	Health status (EQ-5D VAS)	Morning stiffness	Fatigue (FACIT-F)	Physical functioning[b] (HAQ-DI)	Health-related quality of life (SF-36v2 acute)	SAEs	Discontinuation due to AEs	Infections[c]	Serious infections[d]
JADV	Y	Y	Y	Y	Y	Y	Y	Y	Y[e]	Y	Y	Y	Y	Y	Y	Y

a: Based on 28 joints.
b: Including activities of daily living.
c: AEs of the SOC "infections and infestations".
d: SAEs of the SOC "infections and infestations".
e: Only for patients for whom a value of the duration in minutes recorded with an ePRO tablet is available at the start of the study.

AE: adverse event; CDAI: Clinical Disease Activity Index; DAS: Disease Activity Score; ePRO: electronic patient-reported outcome; EQ-5D: European Quality of Life-5 Dimensions; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; hsCRP: high-sensitivity C-reactive protein; MTX: methotrexate; RCT: randomized controlled trial; SAE: serious adverse event; SDAI: Simplified Disease Activity Index; SF-36v2: Short Form (36) – version 2 Health Survey; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus; Y: yes

Table 3: Risk of bias at study and outcome level – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (mITT population)

Study		Outcomes															
	Study level	All-cause mortality	Remission (SDAI ≤ 3.3; CDAI ≤ 2.8; Boolean definition)	Low disease activity (DAS28-hsCRP ≤ 3.2; SDAI ≤ 11; CDAI ≤ 10)	Tender joint count[a]	Swollen joint count[a]	Pain (VAS)	Disease activity (VAS)	Health status (EQ-5D VAS)	Morning stiffness	Fatigue (FACIT-F)	Physical functioning[b] (HAQ-DI)	Health-related quality of life (SF-36v2 acute)	SAEs	Discontinuation due to AEs	Infections[c]	Serious infections[d]
JADV	L	H[e]	L	H[f]	H[f]	H[f]	H[f]	H[f]	H[f]	H[e]	H[f]	H[f]	H[f]	H[e]	H[e]	H[e]	H[e]

a: Based on 28 joints.
b: Including activities of daily living.
c: AEs of the SOC "infections and infestations".
d: SAEs of the SOC "infections and infestations".
e: Unclear proportion of LOCF-imputed values.
f: High proportion of LOCF- or NRI-imputed values in the intervention arm (at least 19.1%) and in the comparator arm (at least 27%).

AE: adverse event; DAS: Disease Activity Score; EQ-5D: European Quality of Life-5 Dimensions; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; H: high; HAQ-DI: Health Assessment Questionnaire-Disability Index; hsCRP: high-sensitivity C-reactive protein; L: low; LOCF: last observation carried forward; MTX: methotrexate; NRI: non-responder imputation; RCT: randomized controlled trial; SAE: serious adverse event; SDAI: Simplified Disease Activity Index; SF-36v2: Short Form (36) – version 2 Health Survey; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The assessment of the risk of bias at outcome level for the mITT population concurs with that of the relevant subpopulations for all outcomes [1]: The risk of bias for the outcome "remission" was rated as low; the risk of bias for all other outcomes was rated as high due a high or unclear proportion of imputed values.

Table 4 and Table 5 summarize the results on the comparison of baricitinib + MTX with adalimumab + MTX based on the mITT population.

Table 4: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (mITT population)

Study Outcome category Outcome	Baricitinib + MTX		Adalimumab + MTX		Baricitinib + MTX vs. adalimumab + MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR[a] [95% CI]; p-value
JADV (week 52)					
Mortality					
All-cause mortality	487	2 (0.4)	330	1 (0.3)	POR: 1.34 [0.13; 13.50]; 0.907[b]
Morbidity					
Remission					
SDAI ≤ 3.3	487	110 (22.6)	330	59 (17.9)	1.26 [0.96; 1.67]; 0.101[d]
CDAI ≤ 2.8	487	105 (21.6)	330	58 (17.6)	1.23 [0.92; 1.64][e]; 0.197[b]
Boolean definition[c]	487	76 (15.6)	330	43 (13.0)	1.20 [0.85; 1.69][e]; 0.343[b]
Low disease activity					
DAS28-hsCRP ≤ 3.2	487	271 (55.6)	330	159 (48.2)	1.14 [1.00; 1.30]; 0.059[d]
SDAI ≤ 11	487	278 (57.1)	330	163 (49.4)	1.16 [1.01; 1.32][e]; 0.031[b]
CDAI ≤ 10	487	277 (56.9)	330	163 (49.4)	1.14 [1.00; 1.29]; 0.055[d]
Physical functioning (HAQ-DI[f])	487	329 (67.6)	330	192 (58.2)	1.14 [1.03; 1.27]; 0.016[d]
Health-related quality of life					
SF-36v2 acute					
Physical Component Summary[g]	487	292 (60.0)	330	171 (51.8)	1.14 [1.00; 1.29]; 0.047[d]
Mental Component Summary[g]	487	166 (34.1)	330	97 (29.4)	1.14 [0.93; 1.39]; 0.219[d]

(continued)

Table 4: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (mITT population) (continued)

Study Outcome category Outcome	Baricitinib + MTX		Adalimumab + MTX		Baricitinib + MTX vs. adalimumab + MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR[a] [95% CI]; p-value
JADV (week 52)					
Side effects					
AEs (supplementary information)	487	384 (78.9)	330	253 (76.7)	–
SAEs	487	38 (7.8)	330	13 (3.9)	1.98 [1.07; 3.66]; 0.027[b]
Discontinuation due to AEs[h]	487	34 (7.0)	330	14 (4.2)	1.65 [0.90; 3.02]; 0.115[b]
Infections[i]	487	233 (47.8)	330	145 (43.9)	1.09 [0.93; 1.27]; 0.343[b]
Serious Infections[j]	487	10 (2.1)	330	5 (1.5)	1.36 [0.47; 3.93][e]; 0.611[b]

a: Unless stated otherwise.
b: Institute's calculation, unconditional exact test (CSZ method according to [5]).
c: Number of tender and swollen joints each ≤ 1, CRP ≤ 1 mg/dL, assessment of disease activity by the patient ≤ 1.
d: According to the company calculated using an adjusted logistic regression model; missing data were imputed using NRI.
e: Institute's calculation of effect and CI (asymptotic).
f: Patients with improvement by ≥ 0.22.
g: Patients with improvement by ≥ 5 points.
h: Treatment discontinuation due to AEs, without deaths.
i: AEs with PTs cited in the SOC "infections and infestations" in MedDRA V18.0.
j: SAEs with PTs cited in the SOC "infections and infestations" in MedDRA V18.0.

AE: adverse event; CI: confidence interval; DAS: Disease Activity Score; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; hsCRP: high-sensitivity C-reactive protein; MedDRA: Medical Dictionary for Regulatory Activities; MTX: methotrexate; n: number of patients with (at least 1) event; N: number of analysed patients; ND: no data; NRI: non-responder imputation; POR: Peto odds ratio; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SDAI: Simplified Disease Activity Index; SF-36v2: Short Form (36) – version 2 Health Survey; SOC: System Organ Class; vs.: versus

Table 5: Results (morbidity, continuous) – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (mITT population)

Study Outcome category	Baricitinib + MTX			Adalimumab + MTX			Baricitinib + MTX vs. adalimumab + MTX
Outcome	**N[a]**	**Values at start of study mean (SD)[b]**	**Change at end of study mean (SD)[b]**	**N[a]**	**Values at start of study mean (SD)[b]**	**Change at end of study mean (SD)[b]**	**LSMD [95% CI]; p-value[b,c]**
JADV (week 52)							
Morbidity							
Tender joint count[d]	483	14.0 (6.6)	–10.0 (7.1)	328	13.9 (6.9)	-9.0 (7.3)	–0.9 [–1.6; –0.1]; 0.032[e]
Swollen joint count[d]	483	11.1 (5.0)	–8.2 (5.7)	328	11.2 (5.6)	–7.4 (5.8)	–0.9 [–1.5; –0.2]; 0.007[f]
Pain (VAS)	482	61.8 (21.8)	–36.8 (27.9)	327	61.0 (22.7)	–30.4 (27.7)	–5.9 [–9.1; –2.6]; < 0.001 Hedges' g: –0.25 [–0.40; –0.11][g]
Disease activity (VAS)	482	63.1 (21.2)	–36.7 (27.4)	327	63.7 (21.2)	–31.2 (27.2)	–6.0 [–9.2; –2.8]; < 0.001 Hedges' g: –0.26 [–0.40; –0.12][g]
Health status (EQ-5D VAS)	479	50.9 (20.1)	19.9 (28.0)	320	50.3 (21.5)	13.3 (29.7)	7.4 [4.2; 10.7]; < 0.001 Hedges' g: 0.32 [0.18; 0.46][g]
Morning stiffness[h]	277	Median: 60.0	Median: –50.0 95% CI: [−60.0; −30.0]	190	Median: 60.0	Median: –22.0 95% CI: [−32.0; −13.0]	Median of the differences[i]: −13.0 [−30.0; 0.0][j]; 0.033[k]
Fatigue (FACIT-F)	479	28.1 (10.7)	10.8 (10.9)	320	27.6 (11.4)	9.8 (10.8)	1.3 [0.1; 2.6]; 0.033 Hedges' g: 0.15 [0.01; 0.29][g]

(continued)

Table 5: Results (morbidity, continuous) – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (mITT population) (continued)

a: Number of patients considered in the analysis for the calculation of the effect estimate. The values at the start of the study may be based on other patient numbers.
b: Unless stated otherwise.
c: LSMD, 95% CI and p-value from ANCOVA, missing data were imputed using mLOCF.
d: Based on 28 joints.
e: Hedges' g: −0.1 [−0.3; 0.0].
f: Hedges' g: −0.2 [−0.3; −0.0].
g: Institute's calculation based on the LSMD and the SE from the ANCOVA.
h: Patients for whom a value of the duration in minutes recorded with an ePRO tablet is available at the start of the study.
i: Primarily planned non-parametric estimation method, missing data were imputed using mLOCF. Results from the sensitivity analysis from ANCOVA (missing values imputed using mLOCF): −27.34 (−51.35; −3.32); p = 0.026; Hedges' g: −0.18 [−0.36; 0.01] [Institute's calculation].
j: Hodges-Lehmann estimator.
k: Wilcoxon rank sum test.
ANCOVA: analysis of covariance; CI: confidence interval; ePRO: electronic patient-reported outcome; EQ-5D: European Quality of Life-5 Dimensions; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; LSMD: least squares mean distance; MTX: methotrexate; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

One relevant study was available for the assessment of the added benefit of baricitinib. In view of the low risk of bias, at most an indication of an effect can be derived for the outcome "remission". For all other outcomes, at most hints of an effect can be derived due to the high risk of bias.

Hereinafter, effects in favour of baricitinib + MTX are referred to as "positive effects" and effects to the disadvantage of baricitinib + MTX are referred to as "negative effects".

Mortality

All-cause mortality

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an effect of baricitinib + MTX in comparison with adalimumab + MTX for this outcome.

Morbidity

Remission

No statistically significant difference between the treatment groups was shown for the outcome "remission" for any of the operationalizations (Simplified Disease Activity Index [SDAI] ≤ 3.3; Clinical Disease Activity Index [CDAI] ≤ 2.8; Boolean definition). This resulted in no hint of an effect of baricitinib + MTX in comparison with adalimumab + MTX for this outcome.

Low disease activity

A statistically significant difference in favour of baricitinib + MTX was shown for the outcome "low disease activity (Disease Activity Score 28 high-sensitivity C-reactive protein [DAS28-hsCRP] ≤ 3.2; SDAI ≤ 11; CDAI ≤ 10)" for the operationalization "SDAI ≤ 11". The effect estimates of the operationalizations DAS28-hsCRP ≤ 3.2 and CDAI ≤ 10 were of a similar magnitude; the significance level of $p < 0.05$ was slightly exceeded. This resulted in a hint of a positive effect of baricitinib + MTX in comparison with adalimumab + MTX for this outcome.

Tender and swollen joint count

For the outcomes "tender joint count" and "swollen joint count", a statistically significant difference in favour of baricitinib + MTX was shown for the mean change. The mean difference in both outcomes was fewer than 1 joint. This group difference was not relevant. This was supported by consideration of the standardized mean difference in the form of Hedges' g (the 95% confidence intervals [CIs] did not lie completely below the irrelevance threshold of −0.2). This resulted in no hint of a relevant effect of baricitinib + MTX in comparison with adalimumab + MTX for these outcomes.

Pain (VAS)

For the outcome "pain" (visual analogue scale [VAS]), a statistically significant difference in favour of baricitinib + MTX was shown for the mean change. The standardized mean difference in the form of Hedges' g was considered to check the relevance of the result. The 95% CI was not completely below the irrelevance threshold of –0.2. It can therefore not be inferred that the effect is relevant. This resulted in no hint of an effect of baricitinib + MTX in comparison with adalimumab + MTX for this outcome.

Disease activity (VAS)

For the outcome "disease activity" (VAS), a statistically significant difference in favour of baricitinib + MTX was shown for the mean change. The standardized mean difference in the form of Hedges' g was considered to check the relevance of the result. The 95% CI was not completely below the irrelevance threshold of –0.2. It can therefore not be inferred that the effect is relevant. This resulted in no hint of an effect of baricitinib + MTX in comparison with adalimumab + MTX for this outcome.

Health status (EQ-5D VAS)

For the outcome "health status" (European Quality of Life-5 Dimensions [EQ-5D] VAS), a statistically significant difference in favour of baricitinib + MTX was shown for the mean change. The standardized mean difference in the form of Hedges' g was considered to check the relevance of the result. The 95% CI was not completely above the irrelevance threshold of 0.2. It can therefore not be inferred that the effect is relevant. This resulted in no hint of an effect of baricitinib + MTX in comparison with adalimumab + MTX for this outcome.

Morning stiffness

A statistically significant difference in favour of baricitinib + MTX was shown for the outcome "morning stiffness" for the median of the differences (primarily planned type of analysis). The upper CI limit of the effect estimate was very close to the zero effect. It cannot be derived from the median of the differences that there was a relevant effect. This was supported by the additional sensitivity analysis with their standardized mean difference in the form of Hedges' g (the 95% CI did not lie completely below the irrelevance threshold of −0.2). This resulted in no hint of a relevant effect of baricitinib + MTX in comparison with adalimumab + MTX for this outcome.

Fatigue (FACIT-F)

For the outcome "fatigue", a statistically significant difference in favour of baricitinib + MTX was shown for the mean change. The standardized mean difference in the form of Hedges' g was considered to check the relevance of the result. The 95% CI was not completely above the irrelevance threshold of 0.2. It can therefore not be inferred that the effect is relevant. This resulted in no hint of an effect of baricitinib + MTX in comparison with adalimumab + MTX for this outcome.

Physical functioning (HAQ-DI)

A statistically significant difference in favour of baricitinib + MTX was shown for the outcome "physical functioning" (improvement in Health Assessment Questionnaire-Disability Index [HAQ-DI] by ≥ 0.22 points). This resulted in a hint of a positive effect of baricitinib + MTX in comparison with adalimumab + MTX for this outcome.

Health-related quality of life

SF-36v2 acute – Physical Component Summary

A statistically significant difference in favour of baricitinib + MTX was shown for the Physical Component Summary of the Short Form (36) – version 2 Health Survey [SF-36v2] acute (improvement by ≥ 5 points). This resulted in a hint of a positive effect of baricitinib + MTX in comparison with adalimumab + MTX for this outcome.

SF-36v2 acute – Mental Component Summary

No statistically significant difference between the treatment groups was shown for the Mental Component Summary of the SF-36v2 acute (improvement by ≥ 5 points). This resulted in no hint of an effect of baricitinib + MTX in comparison with adalimumab + MTX for this outcome.

Side effects

Serious adverse events

A statistically significant difference to the disadvantage of baricitinib + MTX was shown for the outcome "serious adverse events (SAEs)". This resulted in a hint of a negative effect of baricitinib + MTX in comparison with adalimumab + MTX for this outcome.

Discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to adverse events (AEs)" (treatment discontinuation due to AEs). This resulted in no hint of an effect of baricitinib + MTX in comparison with adalimumab + MTX for this outcome.

Infections

No statistically significant difference between the treatment groups was shown for the outcome "infections" (AEs of the System Organ Class [SOC] "infections and infestations"). This resulted in no hint of an effect of baricitinib + MTX in comparison with adalimumab + MTX for this outcome.

Serious infections

No statistically significant difference between the treatment groups was shown for the outcome "serious infections" (SAEs of the SOC "infections and infestations"). This resulted in no hint of an effect of baricitinib + MTX in comparison with adalimumab + MTX for this outcome.

Specific adverse events

All AEs with a frequency of ≥ 5% in at least 1 of the study arms as well as all SAEs and discontinuations due to AEs with a frequency of ≥ 1% are presented as additional information in Appendix A (Table 10 to Table 12). There were no notable differences between the groups.

Subgroups and other effect modifiers

The same subgroup characteristics were considered relevant for the assessment of the mITT population as in assessment A17-14 [1].

Hereinafter, only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented [6]. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least 1 subgroup.

Table 6 and Table 7 summarize the subgroup analyses on the comparison of baricitinib + MTX with adalimumab + MTX for the mITT population.

Table 6: Subgroups (morbidity) – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (mITT population)

Study Outcome Characteristic Subgroup	Baricitinib + MTX			Adalimumab + MTX			Baricitinib + MTX vs. adalimumab + MTX
	N[a]	Values at start of study mean (SD)	Change at end of study LSM (SE)	N[a]	Values at start of study mean (SD)	Change at end of study LSM (SE)	LSMD [95% CI]; p-value[b]
JADV (week 52)							
Disease activity (VAS)							
Joint erosion status							
1-2 joint erosions + seropositivity	115	62.46 (24.05)	–35.82 (2.05)	80	64.08 (21.84)	–35.58 (2.45)	–0.24 [–6.54; 6.07]; 0.941
≥ 3 joint erosions	366	63.29 (20.21)	–37.29 (1.22)	244	64.06 (20.83)	–29.47 (1.50)	–7.82 [–11.61; –4.03]; < 0.001
Total					Interaction:		p-value = 0.043

a: Number of patients considered in the analysis for the calculation of the effect estimate. The values at the start of the study may be based on other patient numbers.
b: LSMD, 95% CI and p-value from ANCOVA.

ANCOVA: analysis of covariance; CI: confidence interval; LSM: least squares mean; LSMD: least-square mean difference; MTX: methotrexate; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Table 7: Subgroups (side effects) – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (mITT population)

Study Outcome Characteristic Subgroup	Baricitinib + MTX		Adalimumab + MTX		Baricitinib + MTX vs. adalimumab + MTX	
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
JADV (week 52)						
Side effects						
SAEs						
Joint erosion status						
1-2 joint erosions + seropositivity	115	4 (3.5)	82	5 (6.1)	0.57 [0.16; 2.06][a]	ND
≥ 3 joint erosions	371	34 (9.2)	245	8 (3.3)	2.81 [1.32; 5.96][a]	ND
Total					Interaction:	0.036[a]

a: Institute's calculation.

CI: confidence interval; MTX: methotrexate; n: number of patients with (at least 1) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Disease activity (VAS)

There was proof of an effect modification by the characteristic "joint erosion status" for the outcome "disease activity (VAS)". There was no statistically significant difference between the treatment groups for patients with 1 to 2 joint erosions and seropositivity. A statistically significant difference in favour of baricitinib + MTX was shown for patients with ≥ 3 joint erosions.

The fact that there was no effect modification for the subgroup characteristic "disease activity" (DAS28-hsCRP ≤ 5.1/> 5.1) was also considered in the evaluation of the effects. Hence overall, there was no effect modification that occurred consistently across the characteristics influencing the course of disease (joint erosion status and disease activity). No separate derivation of effects by subgroups was therefore conducted for this outcome.

Serious adverse events

There was proof of an effect modification by the characteristic "joint erosion status" for the outcome "SAEs". There was no statistically significant difference between the treatment groups for patients with 1 to 2 joint erosions and seropositivity. A statistically significant difference to the disadvantage of baricitinib + MTX was shown for patients with ≥ 3 joint erosions.

The fact that there was no effect modification for the subgroup characteristic "disease activity" (DAS28-hsCRP ≤ 5.1/> 5.1) was also considered in the evaluation of the effects. Hence overall, there was no effect modification that occurred consistently across the characteristics influencing the course of disease (joint erosion status and disease activity). No separate derivation of effects by subgroups was therefore conducted for this outcome.

2.1.3 Probability and extent of the effects based on the mITT population

The derivation of probability and extent of the effects is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [6].

The procedure for deriving an overall conclusion on the effects observed in the mITT population of the JADV study based on the aggregation of the conclusions deduced at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

Assessment of the effects at outcome level

The data presented in Table 4 and Table 5 resulted in the following assessment of baricitinib + MTX in comparison with adalimumab + MTX for the mITT population of the JADV study:

- a hint of a positive effect for each of the outcomes "low disease activity", "physical functioning (HAQ-DI)" and "Physical Component Summary of the SF-36v2 acute"
- a hint of negative effect for the outcome "SAEs"

The extent of the respective effect at outcome level was estimated from these results (see Table 8).

Table 8: Extent of the effects at outcome level: baricitinib + MTX vs. adalimumab + MTX (mITT population)

Outcome category **Outcome**	**Baricitinib + MTX vs. adalimumab + MTX** **Proportion of patients with event or change** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	Proportion: 0.4% vs. 0.3% POR: 1.34 [0.13; 13.5]; p = 0.907	Effect not proven
Morbidity		
Remission		
SDAI ≤ 3.3	Proportion: 22.6% vs. 17.9% RR: 1.26 [0.96; 1.67]; p = 0.101	Effect not proven
CDAI ≤ 2.8	Proportion: 21.6% vs. 17.6% RR: 1.23 [0.92; 1.64]; p = 0.197	
Boolean definition	Proportion: 15.6% vs. 13.0% RR: 1.20 [0.85; 1.69]; p = 0.343	
Low disease activity		
DAS28-hsCRP ≤ 3.2	Proportion: 55.6% vs. 48.2% RR: 1.14 [1.00; 1.30]; p = 0.059	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ positive effect, extent: “minor”
SDAI ≤ 11	Proportion: 57.1% vs. 49.4% RR: 1.16 [1.01; 1.32]; p = 0.031 RR: 0.86 [0.76; 0.99][c]	
CDAI ≤ 10	Proportion: 56.9% vs. 49.4% RR: 1.14 [1.00; 1.29]; p = 0.055 probability: “hint”	
Tender joint count[d]	Mean: –10.0 vs. –9.0 LSMD: –0.9 [–1.6; –0.1]; p = 0.032[e]	Relevant effect not proven
Swollen joint count[d]	Mean: –8.2 vs. –7.4 LSMD: –0.9 [–1.5; –0.2]; p = 0.007[e]	Relevant effect not proven
Pain (VAS)	Mean: –36.8 vs. –30.4 LSMD: −5.9 [−9.1; −2.6]; p < 0.001 Hedges’ g: –0.25 [–0.40; –0.11][f]	Relevant effect not proven
Disease activity (VAS)	Mean: –36.7 vs. –31.2 LSMD: –6.0 [–9.2; –2.8]; p < 0.001 Hedges’ g: –0.26 [–0.40; –0.12][f]	Relevant effect not proven
Health status (EQ-5D VAS)	Mean: 19.9 vs. 13.3 LSMD: 7.4 [4.2; 10.7]; p < 0.001 Hedges’ g: 0.32 [0.18; 0.46][f]	Relevant effect not proven

(continued)

Table 8: Extent of the effects at outcome level: baricitinib + MTX vs. adalimumab + MTX (mITT population) (continued)

Morning stiffness[g]	Median: –50.0 vs. –22.0 Median of the differences: –13.0 [–30.0; 0.0]; p = 0.033[e]	Relevant effect not proven
Fatigue (FACIT-F)	Mean: 10.8 vs. 9.8 LSMD: 1.3 [0.1; 2.6]; p = 0.033 Hedges' g: 0.15 [0.01; 0.29][f]	Relevant effect not proven
Physical functioning (HAQ-DI[h])	Proportion: 67.6% vs. 58.2% RR: 1.14 [1.03; 1.27]; p = 0.016 RR: 0.88 [0.79; 0.97][c] probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ positive effect, extent: "minor"
Health-related quality of life		
SF-36v2 acute, Physical Component Summary[i]	Proportion: 60.0% vs. 51.8% RR: 1.14 [1.00; 1.29]; p = 0.047 RR: 0.88 [0.78; 1.00][c] probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ positive effect, extent: "minor"
SF-36v2 acute, Mental Component Summary[i]	Proportion: 34.1% vs. 29.4% RR: 1.14 [0.93; 1.39]; p = 0.219	Effect not proven
Side effects		
Serious adverse events	Proportion: 7.8% vs. 3.9% RR: 1.98 [1.07; 3.66]; p = 0.027 RR: 0.51 [0.27; 0.93][c] probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ negative effect, extent: "minor"
Discontinuation due to AEs	Proportion: 7.0% vs. 4.2% RR: 1.65 [0.90; 3.02]; p = 0.115	Effect not proven
Infections	Proportion: 47.8% vs. 43.9% RR: 1.09 [0.93; 1.27]; p = 0.343	Effect not proven
Serious Infections	Proportion: 2.1% vs. 1.5% RR: 1.36 [0.47; 3.93]; p = 0.611	Effect not proven

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the effects.
d: Based on 28 joints.
e: The presence of a relevant effect cannot be derived.
f: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, it cannot be derived that a relevant effect is present.
g: Patients for whom a value of the duration in minutes recorded with an ePRO tablet is available at the start of the study.
h: Patients with improvement by ≥ 0.22 points.
i: Patients with improvement by ≥ 5 points.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; DAS: Disease Activity Score; ePRO: electronic patient-reported outcome; EQ-5D: European Quality of Life-5 Dimensions; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; hsCRP: high-sensitivity C-reactive protein; LSM: least squares mean; LSMD: least squares mean distance; MTX: methotrexate; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SDAI: Simplified Disease Activity Index; SF-36v2: Short Form (36) – version 2 Health Survey; VAS: visual analogue scale; vs.: versus

Overall conclusion

Table 9 summarizes the results that were considered in the overall conclusion on the effects based on the mITT population.

Table 9: Positive and negative effects from the assessment of baricitinib + MTX in comparison with adalimumab + MTX (mITT population)

Positive effects	**Negative effects**
Serious/severe symptoms/late complications: ▪ Low disease activity: hint of a positive effect – extent: "minor" ▪ Physical functioning (HAQ-DI): hint of a positive effect – extent: "minor" Health-related quality of life: ▪ SF-36v2 acute, Physical Component Summary: hint of a positive effect – extent: "minor"	Serious/severe side effects: ▪ SAEs: hint of a negative effect – extent: "minor"
HAQ-DI: Health Assessment Questionnaire-Disability Index; mITT: modified intention to treat; MTX: methotrexate; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey	

In summary, both positive and negative effects of equal certainty of results were shown for the mITT population. Hints of a positive effect with the extent "minor" were shown in the categories of serious/severe symptoms/late complications and health-related quality of life for the outcomes "low disease activity", "physical functioning" and "SF-36v2 acute (Physical Component Summary)". For the outcome "low disease activity", the p-value was close to the significance level of 0.05 for all 3 operationalizations. This underlines that it was no more than a minor effect. This was offset by a negative effect with the extent "minor" in the category of serious/severe side effects (SAEs).

It is to be noted that 15.5% of the patients in the mITT population could not be allocated to either of both research questions relevant for the benefit assessment because they were treated with another cDMARD in addition to MTX. It is unclear whether it is adequate to use the mITT population for the assessment of the relevant research questions because there was no information that allow assessing the homogeneity between the subpopulations (both relevant subpopulations and the 15.5% of the patients).

In the overall consideration, neither an advantage nor a disadvantage of baricitinib + MTX in comparison with adalimumab + MTX is proven for research questions 2 and 3 based on the mITT population.

3 References

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Appendix A – Results on side effects (mITT population)

Table 10: Common AEs (in the SOC and in the PT ≥ 5% in at least 1 study arm) – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (mITT population)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Baricitinib + MTX** **N = 487**	**Adalimumab + MTX** **N = 330**
JADV		
Overall rate of AEs	384 (78.9)	253 (76.7)
Blood and lymphatic system disorders	43 (8.8)	22 (6.7)
Gastrointestinal disorders	108 (22.2)	64 (19.4)
General disorders and administration site conditions	29 (6.0)	27 (8.2)
Infections and infestations	233 (47.8)	145 (43.9)
Nasopharyngitis	59 (12.1)	48 (14.5)
Urinary tract infection	33 (6.8)	18 (5.5)
Bronchitis	31 (6.4)	13 (3.9)
Upper respiratory tract infection	27 (5.5)	16 (4.8)
Pharyngitis	16 (3.3)	18 (5.5)
Injury, poisoning and procedural complications	49 (10.1)	27 (8.2)
Investigations	73 (15.0)	41 (12.4)
Metabolism and nutrition disorders	54 (11.1)	23 (7.0)
Musculoskeletal and connective tissue disorders	75 (15.4)	45 (13.6)
Nervous system disorders	44 (9.0)	27 (8.2)
Respiratory, thoracic and mediastinal disorders	48 (9.9)	28 (8.5)
Skin and subcutaneous tissue disorders	34 (7.0)	40 (12.1)
Vascular disorders	26 (5.3)	31 (9.4)

a: MedDRA version 18.0.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 11: Common SAEs (in the SOC and in the PT ≥ 1% in at least 1 study arm) – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (mITT population)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Baricitinib + MTX** **N = 487**	**Adalimumab + MTX** **N = 330**
JADV		
Overall rate of SAEs	38 (7.8)	13 (3.9)
Infections and infestations	10 (2.1)	5 (1.5)
Injury, poisoning and procedural complications	5 (1.0)	1 (0.3)

a: MedDRA version 18.0.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 12: Common discontinuations due to AEs (including deaths) (in the SOC and in the PT ≥ 1% in at least 1 study arm) – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (mITT population)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Baricitinib + MTX** **N = 487**	**Adalimumab + MTX** **N = 330**
JADV		
Overall rate of discontinuations due to AEs	36 (7.4)	15 (4.5)
Infections and infestations	14 (2.9)	7 (2.1)
Herpes zoster	9 (1.8)	5 (1.5)

a: MedDRA version 18.0.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus