IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A17-14

Baricitinib (rheumatoid arthritis) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.8 of the dossier assessment *Baricitinib (Rheumatoide Arthritis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 June 2017). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables[3]

Page

[3] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACPA	anti-citrullinated protein antibody
ACR	American College of Rheumatology
ACR20	20% improvement in American College of Rheumatology criteria
ACT	appropriate comparator therapy
AE	adverse event
bDMARD	biologic disease-modifying antirheumatic drug
CDAI	Clinical Disease Activity Index
cDMARD	conventional disease-modifying antirheumatic drug
CI	confidence interval
DAS	Disease Activity Score
DAS28-hsCRP	Disease Activity Score 28 high-sensitivity C-reactive protein
DMARD	disease-modifying antirheumatic drug
eGFR	estimated glomerular filtration rate
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HAQ-DI	Health Assessment Questionnaire-Disability Index
hsCRP	high-sensitivity C-reactive protein
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
mITT population	modified intention-to-treat population
MTX	methotrexate
NRI	non-responder imputation
Peto OR	Peto odds ratio
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
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug baricitinib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 31 March 2017.

Research question

The aim of the present report was to assess the added benefit of baricitinib in comparison with the appropriate comparator therapy (ACT) in the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who have not tolerated prior treatment with 1 or more disease-modifying antirheumatic drugs (DMARDs). Baricitinib may be used as monotherapy or in combination with methotrexate (MTX).

The G-BA differentiated between 4 patient groups in its specification of the ACT in the approved therapeutic indication. Four research questions resulted from this for the assessment; their therapeutic indications and ACTs are presented in Table 2.

Table 2: Research questions of the benefit assessment of baricitinib

Research question	**Therapeutic indication**	**ACT**[a, b]
1	Patients without poor prognostic factors[c] who have responded inadequately to prior treatment with 1 disease-modifying antirheumatic drug (conventional DMARDs, including MTX)	Alternative conventional DMARDs if suitable (e.g. MTX, leflunomide) as monotherapy or combination therapy
2	Patients with poor prognostic factors[c] who have responded inadequately to prior treatment with 1 disease-modifying antirheumatic drug (conventional DMARDs, including MTX)	bDMARD in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in MTX intolerance
3	Patients who have responded inadequately to prior treatment with several disease-modifying antirheumatic drugs (conventional DMARDs, including MTX)	bDMARD in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in MTX intolerance
4	Patients who have responded inadequately to prior treatment with 1 or several bDMARDs	Switching of bDMARD treatment (adalimumab or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab; in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in MTX intolerance; or in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on prior therapy Depending on prior therapy, switching the mechanism of action should be considered.

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: After prior therapy with already 2 drugs of one class, continuation of treatment with the same drug class has to be justified based on the underlying medical rationale.
c: Poor prognostic factors: detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DAS: Disease Activity Score; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate

The company followed the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results

Study pool

The study pool for the benefit assessment of baricitinib in comparison with the ACT consisted of the RCT JADV (also called "RA-BEAM" by the company). The study compared baricitinib + MTX with adalimumab + MTX. Due to its design and the patients included, the JADV study was suitable for the derivation of conclusions on the added benefit of baricitinib for the research questions 2 and 3 on the basis of subpopulations.

For research questions 1 and 4, no direct evidence was available for the benefit assessment of baricitinib in comparison with the ACT. An added benefit is therefore not proven.

Research questions 2 and 3

Study characteristics

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). The patients were randomly allocated to treatment with baricitinib or adalimumab or placebo in a ratio of 3:2:3. Randomization was stratified by region and joint erosion status. All patients had poor prognostic factors.

Treatment with baricitinib and adalimumab was in compliance with the approval. The individual stable MTX dosage of the last 8 weeks before study inclusion was continued in both arms.

The planned treatment period was 52 weeks. From week 16, patients with inadequate response in both arms received rescue therapy. Until week 52, the rescue therapy consisted of baricitinib.

Relevant subpopulations for research questions 2 and 3

The subpopulation of patients with poor prognostic factors and inadequate response to prior treatment with 1 conventional DMARD (cDMARD) was relevant for research question 2. This relevant subpopulation of the JADV study (patients who showed inadequate response only to the cDMARD MTX) comprised 243 patients in the intervention arm and 153 patients in the comparator arm.

For research question 3, the subpopulation of patients in the JADV study with inadequate response to prior treatment with several cDMARDs was relevant. In addition, the patients of this relevant subpopulation were not allowed to have been treated with several cDMARDs during the study. This relevant subpopulation comprised 170 patients in the intervention arm and 124 patients in the comparator arm.

Risk of bias

The risk of bias at study level was rated as low. At outcome level, the risk of bias for research questions 2 and 3 for the outcome "remission" was rated as low. It was rated as high for all further outcomes used for which analyses were available for the relevant subpopulations.

Results for research question 2: patients with poor prognostic factors and inadequate response to pretreatment with 1 conventional DMARD

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 added benefit can be derived for the outcome "remission". For all other outcomes, at most hints of an added benefit can be derived due to the high risk of bias.

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 added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

Morbidity

- remission (Simplified Disease Activity Index [SDAI] ≤ 3.3)
- low disease activity (Disease Activity Score 28 high-sensitivity C-reactive protein [DAS28-hsCRP] ≤ 3.2)
- physical functioning (Health Assessment Questionnaire-Disability Index [HAQ-DI])
- tender joint count
- swollen joint count
- morning stiffness

No statistically significant or relevant difference between the treatment groups was shown for the following outcomes: remission (SDAI ≤ 3.3), low disease activity (DAS28-hsCRP ≤ 3.2), physical functioning (HAQ-DI improvement by ≥ 0.22 points), tender joint count, swollen joint count and morning stiffness. This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for these outcomes; an added benefit is therefore not proven.

- pain (visual analogue scale [VAS])

For the outcome "pain" (VAS), no statistically significant difference between the treatment groups was shown for the mean change. However, there was proof of an effect modification by the characteristic "sex" for this outcome. For men, there was a hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for the outcome "pain" (VAS).

For women, there was no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit for women is therefore not proven.

- 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% confidence interval (95% CI) was not completely below the irrelevance threshold of −0.2. It can therefore not be inferred that the effect is relevant. However, there was proof of an effect modification by the characteristic "sex" for this outcome. For men, there was a hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for the outcome "disease activity" (VAS). For women, there was no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit for women is therefore not proven.

- health status (European Quality of Life-5 Dimensions [EQ-5D] VAS)

For the outcome "health status" (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. However, there was proof of an effect modification by the characteristic "age" for this outcome. For patients < 65 years, there was a hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for the outcome "health status" (EQ-5D VAS). For patients ≥ 65 years, there was no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit for patients ≥ 65 years is therefore not proven.

- fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F])

The company presented no analyses for the relevant subpopulation for the outcome "fatigue" (FACIT-F). This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

Health-related quality of life

- Short Form (36) – version 2 Health Survey (SF-36v2) acute – physical component summary
- SF-36v2 acute – mental component summary

No statistically significant difference between the treatment groups was shown for the physical and the mental component summary of the SF-36v2 acute (improvement by ≥ 5 points). This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for these outcomes; an added benefit is therefore not proven.

Side effects

- serious adverse events (SAEs)

A statistically significant difference to the disadvantage of baricitinib + MTX was shown for the outcome "SAEs". This resulted in a hint of greater harm of baricitinib + MTX in comparison with adalimumab + MTX for this outcome.

- discontinuation due to adverse events (AEs)
- infections
- serious infections

No statistically significant difference between the treatment groups was shown for any of the following outcomes: discontinuation due to AEs (treatment discontinuation due to AEs, without deaths), infections and serious infections (AEs and SAEs of the System Organ Class [SOC] "infections and infestations"). Hence for these outcomes, there was no hint of greater or lesser harm from baricitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven.

- further specific AEs

The dossier contained no usable data for the relevant subpopulation for the choice of further specific AEs.

Research question 2: Probability and extent of added benefit, patient groups with therapeutically important added benefit[4]

Overall, there are positive and negative effects. On the negative side, there is greater harm with the extent "considerable" in the category "serious/severe side effects" (SAEs). This is accompanied on the side of positive effects by an added benefit with the extent "non-quantifiable" in the category "non-serious/non-severe symptoms/late complications" for men (pain [VAS] and disease activity [VAS]) and for patients < 65 years (health status [EQ-5D VAS]). These effects did not outweigh the greater harm with the extent "considerable" in the respective subgroups.

In summary, there is a hint of lesser benefit of baricitinib in comparison with adalimumab for patients with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with 1 cDMARD (including MTX) and with poor prognostic factors.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].

Results for research question 3: patients with inadequate response to pretreatment with several conventional DMARDs

Mortality

- all-cause mortality

No deaths occurred in any of the 2 treatment groups until treatment week 52. This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for the outcome "mortality"; an added benefit is therefore not proven.

Morbidity

- remission (SDAI ≤ 3.3)
- low disease activity (DAS28-hsCRP ≤ 3.2)
- physical functioning (HAQ-DI)
- tender joint count
- swollen joint count
- pain (VAS)
- disease activity (VAS)
- health status (EQ-5D VAS)
- morning stiffness

No statistically significant or relevant difference between the treatment groups was shown for any of the outcomes mentioned. This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for these outcomes; an added benefit is therefore not proven.

- fatigue (FACIT-F)

The company presented no analyses for the relevant subpopulation for the outcome "fatigue" (FACIT-F). This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

Health-related quality of life

- SF-36v2 acute – physical component summary
- SF-36v2 acute – mental component summary

No statistically significant difference between the treatment groups was shown for the physical and the mental component summary of the SF-36v2 acute (improvement by ≥ 5 points). This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for these outcomes; an added benefit is therefore not proven.

Side effects

- SAEs
- discontinuation due to AEs
- infections
- serious infections

No statistically significant difference between the treatment groups was shown for any of the following outcomes: SAEs, discontinuation due to AEs (treatment discontinuation due to AEs), infections and serious infections (AEs and SAEs of the SOC "infections and infestations"). Hence for these outcomes, there was no hint of greater or lesser harm from baricitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven.

- further specific AEs

The dossier contained no usable data for the relevant subpopulation for the choice of further specific AEs.

Research question 3: probability and extent of added benefit, patient groups with therapeutically important added benefit

Overall, there are neither positive nor negative effects. This resulted in no hint of an added benefit of baricitinib in comparison with the ACT for patients with moderate to severe active rheumatoid arthritis who have responded inadequately to prior treatment with several cDMARDs (including MTX). An added benefit is therefore not proven.

Probability and extent of added benefit – summary

Table 3 presents a summary of the probability and extent of the added benefit of baricitinib.

Table 3: Baricitinib – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT**[a, b]	**Probability and extent of added benefit**
1	Patients without poor prognostic factors[c] who have responded inadequately to prior treatment with 1 disease-modifying antirheumatic drug (conventional DMARDs, including MTX)	Alternative conventional DMARDs if suitable (e.g. MTX, leflunomide) as monotherapy or combination therapy	Added benefit not proven
2	Patients with poor prognostic factors[c] who have responded inadequately to prior treatment with 1 disease-modifying antirheumatic drug (conventional DMARDs, including MTX)[d]	bDMARD in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in MTX intolerance	Hint of lesser benefit
3	Patients who have responded inadequately to prior treatment with several disease-modifying antirheumatic drugs (conventional DMARDs, including MTX)	bDMARD in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in MTX intolerance	Added benefit not proven
4	Patients who have responded inadequately to prior treatment with 1 or several bDMARDs	Switching of bDMARD treatment (adalimumab or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab; in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in MTX intolerance; or in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on prior therapy Depending on prior therapy, switching the mechanism of action should be considered.	Added benefit not proven

(continued)

Table 3: Baricitinib – probability and extent of added benefit (continued)

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: After prior therapy with already 2 drugs of one class, continuation of treatment with the same drug class has to be justified based on the underlying medical rationale.
c: Poor prognostic factors: detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.
d: According to the SPC, baricitinib is also approved for patients who have not tolerated prior treatment with a DMARD. The relevant subpopulation of the included study for the assessment of the added benefit (only patients who have shown inadequate response to MTX) therefore does not completely cover the therapeutic indication. It remains unclear whether the observed effects can be transferred to patients who have not tolerated prior treatment with a DMARD.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DAS: Disease Activity Score; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate; SPC: Summary of Product Characteristics

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of baricitinib in comparison with the ACT in the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who have not tolerated prior treatment with 1 or more DMARDs. Baricitinib may be used as monotherapy or in combination with MTX.

The G-BA differentiated between 4 patient groups in its specification of the ACT in the approved therapeutic indication. Four research questions resulted from this for the assessment; their therapeutic indications and ACTs are presented in Table 4.

Table 4: Research questions of the benefit assessment of baricitinib

Research question	**Therapeutic indication**	**ACT[a, b]**
1	Patients without poor prognostic factors[c] who have responded inadequately to prior treatment with 1 disease-modifying antirheumatic drug (conventional DMARDs, including MTX)	Alternative conventional DMARDs if suitable (e.g. MTX, leflunomide) as monotherapy or combination therapy
2	Patients with poor prognostic factors[c] who have responded inadequately to prior treatment with 1 disease-modifying antirheumatic drug (conventional DMARDs, including MTX)	bDMARD in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in MTX intolerance
3	Patients who have responded inadequately to prior treatment with several disease-modifying antirheumatic drugs (conventional DMARDs, including MTX)	bDMARD in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in MTX intolerance
4	Patients who have responded inadequately to prior treatment with 1 or several bDMARDs	Switching of bDMARD treatment (adalimumab or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab; in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in MTX intolerance; or in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on prior therapy Depending on prior therapy, switching the mechanism of action should be considered.

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: After prior therapy with already 2 drugs of one class, continuation of treatment with the same drug class has to be justified based on the underlying medical rationale.
c: Poor prognostic factors: detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DAS: Disease Activity Score; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate

The company followed the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on baricitinib (status: 2 February 2017)
- bibliographical literature search on baricitinib (last search on 2 February 2017)
- search in trial registries for studies on baricitinib (last search on 2 February 2017)

To check the completeness of the study pool:

- search in trial registries for studies on baricitinib (last search on 13 April 2017)

No additional relevant study was identified from the check.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
JADV[b] (RA-BEAM)	Yes	Yes	No

a: Study for which the company was sponsor.
b: In the following tables, the study is referred to with this abbreviated form.
MTX: methotrexate; RCT: randomized controlled trial; vs.: versus

The study pool for the benefit assessment of baricitinib in comparison with the ACT consisted of the RCT JADV (also referred to as "RA-BEAM" by the company) and concurred with the study pool of the company. The study compared baricitinib + MTX with adalimumab + MTX. Due to its design and the patients included, the JADV study was suitable for the derivation of conclusions on the added benefit of baricitinib for the research questions 2 and 3 on the basis of subpopulations (see also Sections 2.5 and 2.6).

For research questions 2 and 3, only the results of the relevant subpopulation are presented in each case and used for the benefit assessment. This approach deviates from that of the company. The company additionally presented the results of the modified intention-to-treat population (mITT population) and, in case of missing heterogeneity between the results of the subpopulations at outcome level, derived the added benefit on the basis of the mITT population. This approach was not followed (see Section 2.9.2.8.2 of the full dossier assessment).

Concurring with the information provided by the company, no direct evidence was available for the benefit assessment of baricitinib in comparison with the ACT for research questions 1 and 4.

An overview of the data presented by the company on the different research questions of the benefit assessment is shown in Table 6.

Table 6: Baricitinib – overview of the data available for the benefit assessment for each research question

Research question	**Population**	**Data presented**
1	Patients without poor prognostic factors[a] who have responded inadequately to prior treatment with 1 disease-modifying antirheumatic drug (conventional DMARDs, including MTX)	-
2	Patients with poor prognostic factors[a] who have responded inadequately to prior treatment with 1 disease-modifying antirheumatic drug (conventional DMARDs, including MTX)	RCT (subpopulation[b] of the JADV study)
3	Patients who have responded inadequately to prior treatment with several disease-modifying antirheumatic drugs (conventional DMARDs, including MTX)	RCT (subpopulation[c] of the JADV study)
4	Patients who have responded inadequately to prior treatment with 1 or several bDMARDs	-

a: Poor prognostic factors: detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.
b: Referred to as "subpopulation A2" by the company.
c: Referred to as "subpopulation A3" by the company.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DAS: Disease Activity Score; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; RCT: randomized controlled trial

Section 2.5.4 contains a reference list for the study included for research question 2, which is identical for research question 3.

2.4 Research question 1: patients without poor prognostic factors and with inadequate response to pretreatment with 1 conventional DMARD

2.4.1 Results on added benefit (research question 1)

The company presented no data for the assessment of the added benefit of baricitinib in comparison with the ACT for patients without poor prognostic factors who have responded inadequately to prior treatment with 1 DMARD (cDMARDs, including MTX). This resulted in no hint of an added benefit of baricitinib in comparison with the ACT. An added benefit is therefore not proven.

2.4.2 Probability and extent of added benefit (research question 1)

The company presented no data for the assessment of the added benefit of baricitinib in patients without poor prognostic factors who have responded inadequately to prior treatment with 1 cDMARD (including MTX). An added benefit of baricitinib in comparison with the ACT is therefore not proven for these patients.

This concurs with the assessment of the company, which claimed no added benefit for patients without poor prognostic factors who have responded inadequately to prior treatment with 1 cDMARD (including MTX).

2.4.3 List of included studies (research question 1)

Not applicable as the company presented no relevant data for research question 1 for the benefit assessment.

2.5 Research question 2: patients with poor prognostic factors and with inadequate response to pretreatment with 1 conventional DMARD

2.5.1 Study characteristics (research question 2)

Table 7 and Table 8 describe the study used for the benefit assessment.

Table 7: Characteristics of the study included – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 2)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
JADV	RCT, double-blind, parallel	Adult patients with moderate to severe active rheumatoid arthritis ▪ who have shown inadequate response to MTX ▪ who have not received prior treatment with bDMARDs ▪ who were treated with MTX for at least 12 weeks before study inclusion, of which at least 8 weeks before study inclusion with an oral dose of 7.5 to 25 mg/week (or equivalent injectable dose) ▪ whose last CRP or hsCRP value – if available – was ≥6 mg/L ▪ whose eGFR was ≥ 40 mL/min/1.73 m² Patients receiving corticosteroids at a dose of > 10 mg/day prednisone or equivalent were excluded.	Baricitinib + MTX[b] (N = 488)[c] adalimumab + MTX[d] (N = 330) placebo + MTX[e] (N = 489)[c, f] Relevant subpopulation thereof[g]: baricitinib + MTX (n = 243) adalimumab + MTX (n = 153)	Screening: 3 to 42 days before randomization Treatment: 52 weeks[h] Follow-up (for patients not participating in the JADY extension study): 28 days	335 study centres in Argentina, Belgium, Canada, China, Croatia, Czech Republic, France, Germany, Greece, Great Britain, Hungary, Japan, Latvia, Lithuania, Mexico, Netherlands, Poland, Portugal, Romania, Russia, Slovak Republic, Slovenia, Switzerland, South Africa, South Korea, Spain, Taiwan, United States of America 10/2012–9/2015	Primary: ▪ proportion of patients with ACR20 from the start of the study until week 12 in comparison with placebo Secondary: ▪ morbidity ▪ health-related quality of life ▪ AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: 74 patients in this arm were receiving at least 1 further cDMARD at the start of the study.
c: 1 patient in this arm was not treated.
d: 53 patients in this arm were receiving at least 1 further cDMARD at the start of the study.
e: 89 patients in this arm were receiving at least 1 further cDMARD at the start of the study.
f: The arm is not relevant for the assessment and is not shown in the next tables.
g: Patients with poor prognostic factors who have responded inadequately to prior treatment with 1 cDMARD.
h: Patients allocated to placebo + MTX were switched to baricitinib + MTX at week 24.

ACR20: 20% improvement in American College of Rheumatology criteria; AE: adverse event; bDMARD: biologic disease-modifying antirheumatic drug; cDMARD: conventional disease-modifying antirheumatic drug; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; hsCRP: high-sensitivity C-reactive protein; MTX: methotrexate; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 8: Characteristics of the interventions – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 2)

Study	Intervention	Comparison	Prior and concomitant medication
JADV	▪ Baricitinib 2 or 4 mg orally (1 tablet) daily from week 0 to 52 (based on renal function: 2 mg in eGFR ≥ 40 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2; 4 mg in eGFR ≥ 60 mL/min/1.73 m^2) ▪ placebo subcutaneously (injection) every 2 weeks from week 0 to 50	▪ Adalimumab 40 mg subcutaneously (injection) every 2 weeks from week 0 to 50 ▪ placebo orally (1 tablet) daily from week 0 to 52	▪ cDMARD treatment ▫ MTX: continuation of the individual stable dosage of the last 8 weeks before study inclusion (7.5–25 mg) orally (capsule) or subcutaneously (injection) weekly; the dose could be adjusted for safety reasons ▫ NSAIDs allowed (at a stable dose in the last 6 weeks before the planned randomization); dose reduction and discontinuation allowed[c] ▫ continuation of analgesics (without dose increase) allowed; dose reduction and discontinuation allowed[c] ▫ prednisone (or equivalent) up to 10 mg daily allowed at a stable dose from 6 weeks before randomization until during the treatment phase[c]
	From week 16, patients with inadequate response in the intervention and comparator arm receive rescue therapy[a]. These patients receive baricitinib orally (1 tablet) daily[b] in their rescue therapy until week 52. Subcutaneous injections of placebo or adalimumab are no longer administered in the rescue therapy.		

a: Inadequate response at week 16 is defined as lack of improvement by at least 20% in both TJC and SJC, both at week 14 and at week 16 in comparison with the start of the study. At week 16, the IVRS allocated the rescue therapy based on the TJC and SJC values. After week 16, the rescue therapy was offered at the investigator's discretion on the basis of the TJC and SJC values.
b: Baricitinib dosage 2 or 4 mg, based on renal function.
c: From the start of the rescue therapy, new NSAIDs and analgesics and corticosteroids or dose increases of ongoing NSAIDs and analgesics and corticosteroids are allowed.
cDMARD: conventional disease-modifying antirheumatic drug; eGFR: estimated glomerular filtration rate; IVRS: interactive voice response system; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; SJC: swollen joint count; TJC: tender joint count; vs.: versus

The JADV study was a randomized, multicentre, double-blind, parallel-group phase 3 study. It included adult patients with moderate to severe active rheumatoid arthritis with inadequate response to MTX and no prior therapy with bDMARDs.

A total of 1307 patients were randomly allocated to the arms baricitinib + MTX (488 patients), adalimumab + MTX (330 patients), and placebo + MTX (489 patients). Randomization was stratified by region (USA, Canada and rest of the world; Central and South America and Mexico; Europe; Asia) and joint erosion status (1 to 2 joint erosions and seropositivity; at least 3 joint erosions).

In the intervention arm, baricitinib was administered once daily orally as a tablet, which is in compliance with the approval; subcutaneous placebo injection was administered every 2 weeks. In the comparator arm, adalimumab was administered as subcutaneous injection every 2 weeks, which is in compliance with the approval; placebo was administered as a tablet once daily orally. The individual stable MTX dosage of the last 8 weeks before study inclusion was continued in both arms.

The planned treatment period was 52 weeks. From week 16, patients with inadequate response in both arms received rescue therapy. Until week 52, the rescue therapy consisted of baricitinib orally (1 tablet) daily. Subcutaneous injections of placebo (intervention arm) or adalimumab (comparator arm) were no longer administered in the rescue therapy.

Primary outcome of the JADV study was the 20% improvement in American College of Rheumatology (ACR) criteria (ACR20) from the start of the study until week 12. Patient-relevant outcomes on morbidity, health-related quality of life, and AEs were additionally recorded.

Relevant subpopulation for research question 2 and data cut-off used

The subpopulation of patients with poor prognostic factors and inadequate response to prior treatment with 1 cDMARD was relevant for research question 2. Hence the relevant subpopulation of the JADV study comprised patients who showed inadequate response only to the cDMARD MTX (for prognostic factors of the patients, see section on patient characteristics). This relevant subpopulation comprised 243 patients in the intervention arm and 153 patients in the comparator arm. The placebo + MTX arm was not relevant for the present benefit assessment.

For the relevant subpopulation, the company provided results for the data cut-offs at week 24 and at week 52. Since rheumatoid arthritis is a chronic disease with long-term treatment, the data cut-off at week 52 was used for the present benefit assessment.

Patient characteristics

Table 9 and Table 10 show the characteristics of the patients in the relevant subpopulation of the study included.

Table 9: Characteristics of the relevant subpopulation – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 2)

Study Characteristics Category	**Baricitinib + MTX**	**Adalimumab + MTX**
JADV	N[a] = 243	N[a] = 153
Age [years], mean (SD)	54.3 (12.0)	53.7 (12.0)
Sex [F/M], %	73.7/26.3	68.6/31.4
Region, n (%)		
Central and South America and Mexico	92 (37.9)	56 (36.6)
Eastern Europe	42 (17.3)	22 (14.4)
Japan	32 (13.2)	28 (18.3)
USA and Canada	28 (11.5)	18 (11.8)
Western Europe	20 (8.2)	11 (7.2)
Asia (without Japan)	6 (2.5)	2 (1.3)
Rest of the world	23 (9.5)	16 (10.5)
Disease duration: time between first diagnosis and randomization [years], mean (SD)	7.7 (8.9)	6.8 (7.9)
Functional status [HAQ-DI], mean (SD)	1.68 (0.71)	1.63 (0.69)
Tender joint count[b], mean (SD)	24.7 (13.5)	25.3 (14.3)
Swollen joint count[c], mean (SD)	14.7 (7.9)	16.4 (10.6)
Rheumatoid factor status, n (%)		
Positive	220 (90.5)	133 (86.9)
Negative	23 (9.5)	20 (13.1)
ACPA status, n (%)		
Positive	213 (87.7)	135 (88.2)
Negative	25 (10.3)	18 (11.8)
Undetermined	5 (2.1)	0 (0)
DAS28-hsCRP, n (%)		
≤ 3.2	0 (0)	0 (0)
> 3.2 to ≤ 5.1	54 (22.3)	32 (21.1)
> 5.1	188 (77.7)	120 (78.9)
Renal function [eGFR], n (%)		
< 60 mL/min/1.73 m^2	10 (4.1)	6 (3.9)
≥ 60 mL/min/1.73 m^2	233 (95.9)	147 (96.1)
Bone/joint erosion score[d], mean (SD)	23.3 (29.3)	23.9 (26.1)
Joint space narrowing score[e], mean (SD)	16.0 (24.4)	15.0 (22.5)
Patients with adjustment of therapy[f], n (%)	21 (8.6)	24 (15.7)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	29 (11.9)[g]	22 (14.4)[g]

(continued)

Table 9: Characteristics of the relevant subpopulation – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 2) (continued)

a: Number of analysed patients in relevant subpopulation. 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

Table 10: Pretreatment and concomitant treatment of the relevant subpopulation – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 2)

Study Characteristics Category	**Baricitinib + MTX**	**Adalimumab + MTX**
JADV	N[a] = 243	N[a] = 153
Pretreatment: number of cDMARDs, n (%)		
1[b]	243 (100)	153 (100)
2 (including MTX)	0 (0)	0 (0)
≥ 3 (including MTX)	0 (0)	0 (0)
Concomitant treatment at the start of the study		
MTX dose [mg/week], mean (SD)	15.2 (4.2)	15.2 (4.4)
Corticosteroids		
n (%)	127 (52.3)	93 (60.8)
Dose [mg/day], mean (SD)[c]	5.9 (2.5)	6.4 (2.4)

a: Number of analysed patients in relevant subpopulation.
b: According to the inclusion criteria, all patients in the JADV study had inadequate response to MTX. Patients in the relevant subpopulation had no pretreatment with further cDMARDs.
c: Analysis of patients with corticosteroid treatment at the start of the study.
cDMARD: conventional disease-modifying antirheumatic drug; MTX: methotrexate; n: number of patients in the category; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Overall, the patient characteristics between the arms of the JADV study in the relevant subpopulation were balanced. The mean age of the patients was 54 years. Markedly more women (69 to 74%) than men were included in both arms, reflecting the higher prevalence of rheumatoid arthritis in women [3].

A marked majority of patients was seropositive (positive rheumatoid factor and/or positive anti-citrullinated protein antibody [ACPA] serostatus). Additional analyses in Module 5

showed that 227 (93.4%) of the patients in the intervention arm and 144 (94.1%) of the patients in the comparator arm were seropositive. All patients had moderate to high disease activity (DAS28-hsCRP > 3.2). The distribution of these disease characteristics shows that patients in both study arms were patients with poor prognostic factors.

From week 16, 8.6% of the patients in the intervention arm and 15.7% of the patients in the comparator arm received adjustment of therapy due to inadequate response (rescue therapy). These adjustments of therapy were taken into account in the assessment of the risk of bias. There was no information on treatment discontinuations for the relevant subpopulation.

Risk of bias at study level

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 2)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
JADV	Yes	Yes	Yes	Yes	Yes	Yes	Low
MTX: methotrexate; RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for the JADV study was rated as low. This concurs with the company's assessment.

2.5.2 Results on added benefit (research question 2)

2.5.2.1 Outcomes included (research question 2)

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.9.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - remission
  - low disease activity
  - tender joint count
  - swollen joint count
  - pain, measured using a VAS
  - disease activity, measured using a VAS
  - health status, measured using the EQ-5D VAS
  - morning stiffness, measured using the duration
  - fatigue, measured using the FACIT-F
  - physical functioning, measured using the HAQ-DI
- Health-related quality of life
  - measured with the physical and mental component summary of the SF-36v2 acute
- Side effects
  - SAEs
  - discontinuation due to AEs
  - infections
  - serious infections
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) and presented no analyses for the outcome “fatigue” for the relevant subpopulation (see Section 2.9.2.4.3 of the full dossier assessment).

Table 12 shows for which outcomes data were available for the relevant subpopulation of the study included.

Table 12: Matrix of outcomes – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 2)

Study	Outcomes															
	All-cause mortality	Remission (SDAI ≤ 3.3)	Low disease activity (DAS28-hsCRP ≤ 3.2)	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]	N[f]	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.
f: No data available for the relevant subpopulation

AE: adverse event; 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; N: no; 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

2.5.2.2 Risk of bias (research question 2)

Table 13 shows the risk of bias for the relevant outcomes.

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 2)

Study	Study level	Outcomes															
		All-cause mortality	Remission (SDAI ≤ 3.3)	Low disease activity (DAS28-hsCRP ≤ 3.2)	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]	-[g]	H[f]	H[f]	H[e]	H[e]	H[e]	H[e]

c: 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 (18.5%) and in the comparator arm (28.8%).
g: The company presented no analyses for the relevant subpopulation for this outcome.

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

Concurring with the company's assessment, the risk of bias for the outcome "remission" was rated as low. The risk of bias was rated as high for all further outcomes for which analyses were available for the relevant subpopulation.

The risk of bias for the outcomes "all-cause mortality", "morning stiffness", "SAEs" "discontinuation due to AEs", "infections", and "serious infections" was rated as high because the proportion of values imputed using last observation carried forward (LOCF) for these outcomes was unclear. The risk of bias for the outcomes "tender joint count", "swollen joint count", "pain" (VAS), "disease activity" (VAS) and "health status" (EQ-5D VAS) was rated as high because the proportion of LOCF-imputed values was high in the intervention arm (18.5%) and in the comparator arm (28.8%). The risk of bias for the outcomes "low disease activity" (DAS28-hsCRP $\leq$ 3.2), "physical functioning", including activities of daily living (HAQ-DI), and "health-related quality of life" (SF-36v2 acute) was rated as high because the

proportion of values imputed using non-responder imputation (NRI) for these outcomes was high in the intervention arm (18.5%) and in the comparator arm (28.8%). The assessments of the risk of bias at outcome level deviate from those of the company, which rated the risk of bias as low for these outcomes, except for the outcome “serious infections”, which was not used by the company.

Detailed reasons for the assessment of the risk of bias can be found in Section 2.9.2.4.2 of the full dossier assessment.

2.5.2.3 Results (research question 2)

Table 14 and Table 15 summarize the results of the comparison of baricitinib + MTX with adalimumab + MTX in patients with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with 1 cDMARD (including MTX) and poor prognostic factors. Where necessary, the data from the company’s dossier were supplemented by the Institute’s calculations.

The Peto odds ratio (Peto OR) offers a good approximation of the relative risk (RR) in certain situations (see Section 2.9.2.2 of the full dossier assessment). Hence in these situations the Peto OR was calculated as estimator for the RR and used for the assessment.

Table 14: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 2)

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	243	2 (0.8)	153	1 (0.7)	Peto OR: 1.25 [0.12; 12.87]; 0.919[b]
Morbidity					
Remission (SDAI ≤ 3.3)	243	54 (22.2)	153	30 (19.6)	1.16 [0.78; 1.71]; 0.464[c]
Low disease activity (DAS28-hsCRP ≤ 3.2)	243	139 (57.2)	153	76 (49.7)	1.14 [0.95; 1.38]; 0.161[c]
Physical functioning (HAQ-DI[d])	243	163 (67.1)	153	90 (58.8)	1.11 [0.95; 1.29]; 0.180[c]
Health-related quality of life					
SF-36v2 acute					
Physical component summary[e]	243	156 (64.2)	153	82 (53.6)	1.16 [0.98; 1.38]; 0.086[c]
Mental component summary[e]	243	90 (37.0)	153	44 (28.8)	1.28 [0.96; 1.72]; 0.098[c]
Side effects					
AEs (supplementary information)	243	173 (71.2)	153	110 (71.9)	-
SAEs	243	21 (8.6)	153	4 (2.6)	3.31 [1.16; 9.45]; 0.016[b]
Discontinuation due to AEs[f]	243	14 (5.8)	153	7 (4.6)	1.26 [0.52; 3.05]; 0.653[b]
Infections[g]	243	100 (41.2)	153	57 (37.3)	1.10 [0.86; 1.43]; 0.573[b]
Serious infections[h]	243	5 (2.1)[i]	153	2 (1.3)[i]	1.57 [0.31; 8.01][j]; 0.653[b]

(continued)

Table 14: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 2) (continued)

a: Unless stated otherwise.
b: Institute's calculation, unconditional exact test (CSZ method according to [4]).
c: According to the company calculated using a logistic regression model; missing data were imputed using NRI.
d: Patients with improvement by ≥ 0.22 points.
e: Patients with improvement by ≥ 5 points.
f: Treatment discontinuation due to AEs, without deaths.
g: AEs of the SOC "infections and infestations".
h: SAEs of the SOC "infections and infestations".
i: Institute's calculation.
j: Institute's calculation of effect and CI (asymptotic).
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; DAS: Disease Activity Score; HAQ-DI: Health Assessment Questionnaire-Disability Index; hsCRP: high-sensitivity C-reactive protein; MTX: methotrexate; n: number of patients with (at least 1) event; N: number of analysed patients; NRI: non-responder imputation; Peto OR: Peto odds ratio; 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 15: Results (morbidity, continuous) – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 2)

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[c]**
JADV (week 52)							
Morbidity							
Tender joint count[d]	239	14.7 (6.7)	-10.7 (7.5)	153	14.8 (6.8)	-9.8 (7.9)	-0.8 [-2.0; 0.4] 0.184
Swollen joint count[d]	239	10.9 (5.0)	-8.2 (5.6)	153	11.8 (6.0)	-7.9 (6.0)	-0.8 [-1.7; 0.2] 0.117
Pain (VAS)	238	64.0 (22.5)	-36.4 (29.1)	152	62.9 (23.2)	-31.3 (28.6)	-4.6 [-9.6; 0.3] 0.067
Disease activity (VAS)	238	64.8 (22.0)	-36.7 (28.6)	152	64.3 (21.7)	-30.4 (27.1)	-6.0 [-10.8; -1.2] 0.015 Hedges' g: -0.25 [-0.46; -0.05][e]
Health status (EQ-5D VAS)	237	50.5 (20.9)	19.5 (29.3)	148	48.8 (21.5)	13.2 (31.1)	8.3 [3.5; 13.1]; < 0.001 Hedges' g: 0.36 [0.15; 0.57][e]
Morning stiffness[f]	130	Median: 60.0	Median: -40.0 95% CI: [-60.0; -20.0]	78	Median: 60.0	Median: -15.0 95% CI: [-32.0; -10.0]	Median of the differences: -17.0 [-50.0; 0.0][g]; 0.083[h]
Fatigue (FACIT-F)	No usable data[i]						

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, unless stated otherwise.
d: Based on 28 joints.
e: Institute's calculation based on the LSMD and the SE from the ANCOVA.
f: Patients for whom a value of the duration in minutes recorded with an ePRO tablet is available at the start of the study; the median-based analyses are used because these were primarily planned.
g: Hodges-Lehmann estimator.
h: Wilcoxon rank sum test.
i: The company presented no analyses for the relevant subpopulation for this outcome.
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 added benefit can be derived for the outcome "remission". For all other outcomes, at most hints of an added benefit can be derived

due to the high risk of bias (see Section 2.5.2.2 and Section 2.9.2.4.2 of the full dossier assessment). This deviates from the assessment of the company, which rated the risk of bias as low for all outcomes and derived at most indications of an added benefit for all outcomes.

The derivation of the added benefit was based on the results for the relevant subpopulation. This deviates from the approach of the company, which based its derivation of the added benefit for all outcomes on the results of the mITT population (see Section 2.9.2.8.2 of the full dossier assessment).

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 added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company, which analysed this outcome in the framework of SAEs, using the designation "deaths", however.

Morbidity

Remission

No statistically significant difference between the treatment groups was shown for the outcome "remission" (SDAI ≤ 3.3). This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company, which also derived no added benefit for the outcome "remission" (operationalized using the achievement of both an SDAI ≤ 3.3 and a DAS28-hsCRP < 2.6).

For the present benefit assessment, the definition based on the Clinical Disease Activity Index (CDAI) (≤ 2.8) and the Boolean definition (tender joint count ≤ 1 and swollen joint count ≤ 1 and hsCRP ≤ 1 mg/dL and disease activity [VAS from 0 to 10 cm] ≤ 1 cm) were also to be considered for the outcome "remission" according to the ACR/European League Against Rheumatism (EULAR). The corresponding analyses had been planned in the JADV study. The company, however, provided no analyses for the relevant subpopulation for these definitions (see also Section 2.9.2.4.3 of the full dossier assessment). It can therefore not be evaluated for the relevant subpopulation whether the results for the outcome "remission" largely depend on the definition used.

Low disease activity (DAS28-hsCRP ≤ 3.2)

No statistically significant difference between the treatment groups was shown for the outcome "low disease activity" (DAS28-hsCRP ≤ 3.2). This resulted in no hint of an added

benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company, which also derived no added benefit for the outcome "low disease activity" (operationalized using the achievement of both a DAS28-hsCRP < 3.2 and a CDAI ≤ 10).

Tender joint count

For the outcome "tender joint count", no statistically significant difference between the treatment groups was shown for the mean change. This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which claimed an indication of an added benefit on the basis of the mITT population of the JADV study.

Swollen joint count

For the outcome "swollen joint count", no statistically significant difference between the treatment groups was shown for the mean change. This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which claimed an indication of an added benefit on the basis of the mITT population of the JADV study.

Pain (VAS)

For the outcome "pain" (VAS), no statistically significant difference between the treatment groups was shown for the mean change. However, there was proof of an effect modification by the characteristic "sex" for this outcome (see Section 2.5.2.4). For men, there was a hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for the outcome "pain" (VAS). For women, there was no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit for women is therefore not proven.

This deviates from the assessment of the company, which did not consider subgroups in the derivation of the added benefit. In addition, the company used analyses of the proportions of patients with a VAS improvement by both ≥ 10 mm and ≥ 20 mm in its assessment. These response criteria were considered to be unvalidated (see Section 2.9.2.4.3 of the full dossier assessment). On the basis of the responder analyses and on the analysis of the mean change in the mITT population of the JADV study, the company claimed an indication of an added benefit.

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. However, there was proof of an effect modification by the characteristic "sex" for this outcome (see Section 2.5.2.4). For men, there was a hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for the outcome "disease activity" (VAS). For women, there was no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit for women is therefore not proven.

This deviates from the assessment of the company, which did not consider subgroups in the derivation of the added benefit and overall derived no added benefit.

Health status (EQ-5D VAS)

For the outcome "health status" (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. However, there was proof of an effect modification by the characteristic "age" for this outcome (see Section 2.5.2.4). For patients < 65 years, there was a hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for the outcome "health status" (EQ-5D VAS). For patients ≥ 65 years, there was no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit for patients ≥ 65 years is therefore not proven.

This deviates from the assessment of the company, which did not consider subgroups in the derivation of the added benefit. In addition, the company used analyses of the proportions of patients with a VAS improvement by ≥ 10 mm in its assessment. This response criterion was considered to be unvalidated (see Section 2.9.2.4.3 of the full dossier assessment). On the basis of the responder analyses and on the analysis of the mean change in the mITT population of the JADV study, the company claimed an indication of an added benefit.

Morning stiffness

No statistically significant difference between the treatment groups was shown for the outcome "morning stiffness" for the median of the differences (primarily planned type of analysis). This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which – deviating from the primarily planned type of analysis for this outcome – claimed an indication of an added benefit on the basis of the mITT population of the JADV study by analysing the mean change.

Fatigue (FACIT-F)

The company presented no analyses for the relevant subpopulation for the outcome "fatigue" (FACIT-F). This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This deviates from the approach of the company insofar as the company did not use the outcome "fatigue" (FACIT-F) in its assessment.

Physical functioning (HAQ-DI)

No statistically significant difference between the treatment groups was shown for the outcome "physical functioning" (improvement in HAQ-DI by ≥ 0.22 points). This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which claimed an indication of an added benefit for the HAQ-DI on the basis of the mITT population of the JADV study by analysing both the proportions of patients with an improvement by ≥ 0.22 points and the mean change.

Health-related quality of life

SF-36v2 acute – physical component summary

No statistically significant difference between the treatment groups was shown for the physical component summary of the SF-36v2 acute (improvement by ≥ 5 points). This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which claimed an indication of an added benefit on the basis of the mITT population of the JADV study analysing both the proportions of patients with an improvement by ≥ 5 points and the mean change.

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). There was proof of an effect modification by the characteristic "joint erosion status" for this outcome; however, this result did not lead to a separate derivation of the added benefit by subgroups (see Section 2.5.2.4). This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

Serious adverse events

A statistically significant difference to the disadvantage of baricitinib + MTX was shown for the outcome "SAEs". In addition, there was an indication of an effect modification by the

characteristic “joint erosion status” for this outcome; however, this result did not lead to a separate derivation of the added benefit by subgroups (see Section 2.5.2.4). This resulted in a hint of greater harm of baricitinib + MTX in comparison with adalimumab + MTX for this outcome.

This deviates from the approach of the company, which derived an indication of greater risk of harm in the derivation of the added benefit on the basis of the mITT population of the JADV study.

Discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcome “discontinuation due to AEs” (treatment discontinuation due to AEs, without deaths). Hence for this outcome, there was no hint of greater or lesser harm from baricitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven.

This concurs with the company’s assessment.

Infections

No statistically significant difference between the treatment groups was shown for the outcome “infections” (AEs of the SOC “infections and infestations”). Hence for this outcome, there was no hint of greater or lesser harm from baricitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven.

This concurs with the company’s assessment.

Serious infections

No statistically significant difference between the treatment groups was shown for the outcome “serious infections” (SAEs of the SOC “infections and infestations”). Hence for this outcome, there was no hint of greater or lesser harm from baricitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven.

This deviates from the approach of the company insofar as the company did not use the outcome “serious infections” in its assessment.

Further specific adverse events

The dossier contained no usable data for the relevant subpopulation for the choice of further specific AEs (see Section 2.9.2.4.3 of the full dossier assessment).

2.5.2.4 Subgroups and other effect modifiers (research question 2)

The following subgroup characteristics were considered to be relevant for the present benefit assessment (see also Section 2.9.2.4.3 of the full dossier assessment):

- sex (men/women)
- age (< 65/≥ 65 years)
- renal function based on the estimated glomerular filtration rate (eGFR) (< 60/≥ 60 mL/min/1.73 m^2)
- region (USA and Canada/Central and South America and Mexico/Eastern Europe/Western Europe/Asia without Japan/Japan/rest of the world)
- disease activity at the start of the study based on the DAS28-hsCRP (≤ 5.1/> 5.1)
- joint erosion status (stratification factor: 1 to 2 joint erosions + seropositivity/≥ 3 joint erosions)

Due to small sample sizes, the company formed the following categories for the subgroup characteristic "region" for the relevant subpopulation: USA, Canada, rest of the world/Central and South America, Mexico/Europe/Asia. The company conducted no subgroup analyses for the subgroup characteristic "renal function" based on the eGFR. It justified this with the sample size being too small (< 5%) in the subgroup of patients with eGFR < 60 mL/min/1.73 m^2.

For most outcomes included, the company presented subgroup analyses for the relevant subpopulation. The company presented no subgroup analyses for the outcome "all-cause mortality" because it considered the number of deaths to be too small to conduct an informative analysis and subsequent interpretation. The company also conducted no subgroup analyses for the outcomes "fatigue" (FACIT-F) and "serious infections" because it did not include these outcomes in its assessment.

For the remaining outcomes, only the results with at least an indication of an interaction between treatment and subgroup characteristic are presented. The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least 1 subgroup. A relevant effect is not assumed for continuous outcomes if the 95% CI of Hedges' g overlaps with the irrelevance range of [−0.2; 0.2].

The approach of the company deviates insofar as it presented results of individual subgroups for each outcome for the relevant subpopulation only if there was proof of an interaction between treatment and subgroup characteristic. However, the company derived no separate added benefit by subgroups (see Section 2.9.2.4.3 of the full dossier assessment, subgroup characteristics and other effect modifiers).

Table 16 and Table 17 summarize the subgroup analyses of the comparison of baricitinib + MTX with adalimumab + MTX in patients with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with 1 cDMARD (including

MTX) and poor prognostic factors. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 16: Subgroups (health-related quality of life, side effects) – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 2)

Study Outcome	Baricitinib + MTX		Adalimumab + MTX		Baricitinib + MTX vs. adalimumab + MTX	
Characteristic Subgroup	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
JADV (week 52)						
Health-related quality of life						
SF-36v2: mental component summary[a]						
Joint erosion status						
1-2 joint erosions + seropositivity	59	29 (49.2)	40	9 (22.5)	2.18 [1.15; 4.14][b]	0.017[b]
≥ 3 joint erosions	183	61 (33.3)	111	35 (31.5)	1.06 [0.75; 1.49][b]	0.751[b]
Total					Interaction:	0.048
Side effects						
SAEs						
Joint erosion status						
1-2 joint erosions + seropositivity	59	2 (3.4)	40	2 (5.0)	0.68 [0.10; 4.62][c]	0.714[d]
≥ 3 joint erosions	183	19 (10.4)	111	2 (1.8)	5.76 [1.37; 24.27][c]	0.006[d]
Total					Interaction:	0.080[c]

a: Patients with improvement by ≥ 5 points.
b: According to the company calculated using a logistic regression model; missing data were imputed using NRI.
c: Institute's calculation.
d: Institute's calculation, unconditional exact test (CSZ method according to [4]).

CI: confidence interval; CSZ: convexity, symmetry, z score; MTX: methotrexate; n: number of patients with (at least 1) event; N: number of analysed patients; NRI: non-responder imputation; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey; vs.: versus

Table 17: Subgroups (morbidity) – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 2)

Study Outcome	Baricitinib + MTX			Adalimumab + MTX			Baricitinib + MTX vs. adalimumab + MTX
Characteristic Subgroup	N[a]	Values at start of study mean (SD)	Change at end of study LSM[b] (SE)	N[a]	Values at start of study mean (SD)	Change at end of study LSM[b] (SE)	LSMD [95% CI]; p-value[c]
JADV (week 52)							
Pain (VAS)							
Sex							
Male	62	64.60 (24.64)	-42.28 (2.83)	48	61.06 (24.03)	-26.53 (3.22)	-15.75 [-24.26; -7.25]; < 0.001 Hedges' g: -0.69 [-1.08; -0.30]
Female	176	63.90 (21.79)	-33.90 (1.86)	104	63.74 (22.89)	-34.20 (2.42)	0.30 [-5.72; 6.31]; 0.923
Total						Interaction:	p-value = 0.004
Disease activity (VAS)							
Sex							
Male	62	65.42 (22.82)	-43.36 (2.9)	48	67.73 (18.28)	-28.67 (3.29)	-14.69 [-23.39; -5.99]; 0.001 Hedges' g: -0.63 [-1.02; -0.25]
Female	176	64.76 (21.63)	-34.02 (1.78)	104	62.74 (23.00)	-31.72 (2.32)	-2.30 [-8.07; 3.46]; 0.432
Total						Interaction:	p-value = 0.021
Health status (EQ-5D VAS)							
Age							
< 65 years	182	51.12 (21.02)	22.17 (1.78)	122	46.72 (20.72)	11.42 (2.17)	10.75 [5.21; 16.29]; < 0.001 Hedges' g: 0.44 [0.21; 0.68]
≥ 65 years	55	49.38 (20.80)	13.22 (2.93)	26	58.62 (20.80)	16.03 (4.3)	-2.81 [-13.26; 7.64]; 0.594
Total						Interaction:	p-value = 0.029

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: LOCF analysis of the relevant subpopulation.
c: LSMD, 95% CI and p-value from ANCOVA.

ANCOVA: analysis of covariance; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; LSM: least squares mean; LSMD: least squares mean distance; LOCF: last observation carried forward; MTX: methotrexate; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Morbidity

Pain (VAS)

There was proof of an effect modification by the subgroup characteristic "sex" for the outcome "pain" (VAS). A statistically significant difference in favour of baricitinib + MTX, which was rated as relevant (95% CI of Hedges' g fully below the irrelevance threshold of −0.2), was shown for men. This resulted in a hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for men. For women, there was no statistically significant difference between the treatment groups. Hence for women, there was no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX; an added benefit for women is therefore not proven.

This deviates from the approach of the company, which did not consider subgroups in the derivation of the added benefit.

Disease activity (VAS)

There was proof of an effect modification by the subgroup characteristic "sex" for the outcome "disease activity" (VAS). A statistically significant difference in favour of baricitinib + MTX, which was rated as relevant (95% CI of Hedges' g fully below the irrelevance threshold of −0.2), was shown for men. This resulted in a hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for men. For women, there was no statistically significant difference between the treatment groups. Hence for women, there was no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX; an added benefit for women is therefore not proven.

This deviates from the approach of the company, which did not consider subgroups in the derivation of the added benefit.

Health status (EQ-5D VAS)

There was proof of an effect modification by the subgroup characteristic "age" for the outcome "health status" (EQ-5D VAS). A statistically significant difference in favour of baricitinib + MTX, which was rated as relevant (95% CI of Hedges' g fully above the irrelevance threshold of 0.2), was shown for patients < 65 years. This resulted in a hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for patients < 65 years. There was no statistically significant difference between the treatment groups for patients ≥ 65 years. Hence for patients ≥ 65 years, there was no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX; an added benefit for patients ≥ 65 years is therefore not proven.

This deviates from the approach of the company, which did not consider subgroups in the derivation of the added benefit.

Health-related quality of life

SF-36v2 acute – mental component summary

There was proof of an effect modification by the subgroup characteristic "joint erosion status" for the mental component summary of the SF-36v2 acute (improvement by ≥ 5 points). A statistically significant difference in favour of baricitinib + MTX was shown for patients with 1 to 2 joint erosions and seropositivity. There was no statistically significant difference between the treatment groups 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 derivation of the added benefit. 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 the added benefit by subgroups was therefore conducted for this outcome.

This concurs with the company's approach.

Side effects

Serious adverse events

There was an indication of an effect modification by the characteristic "joint erosion status" for the outcome "SAEs".

No statistically significant difference between the treatment groups as well as a deviating direction of effect in comparison with the total relevant subpopulation were shown for patients with 1 to 2 joint erosions and seropositivity. For patients with ≥ 3 joint erosions (as in the total relevant subpopulation), there was a statistically significant difference to the disadvantage of baricitinib + MTX.

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 derivation of the added benefit. 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 the added benefit by subgroups was therefore conducted for this outcome.

This concurs with the company's approach.

2.5.3 Probability and extent of added benefit (research question 2)

The derivation of probability and extent of added benefit is presented below at outcome level for patients with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with 1 cDMARD (including MTX) and poor prognostic factors, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG.

2.5.3.1 Assessment of added benefit at outcome level (research question 2)

The data presented in Section 2.5.2 resulted in the following assessments for baricitinib + MTX in comparison with adalimumab + MTX in patients with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with 1 cDMARD (including MTX) and poor prognostic factors:

- for pain (VAS), a hint of an added benefit in men
- for disease activity (VAS), a hint of an added benefit in men
- for health status (EQ-5D VAS), a hint of an added benefit in patients < 65 years
- for SAEs, a hint of greater harm

Determination of the outcome category for the outcomes "pain" (VAS), "disease activity" (VAS) and "health status" (EQ-5D VAS)

The outcome "disease activity" (VAS) was allocated to the outcome category "non-serious/non-severe symptoms/late complications". This concurs with the assessment of the company, which stated that it had not identified any sources from which a categorization of the VAS of this outcome by severity grade could be inferred.

The outcome "health status" (EQ-5D VAS) was also allocated to the outcome category "non-serious/non-severe symptoms/late complications" because, also for this outcome, the company presented no sources from which a categorization of the VAS of this outcome by severity grade could be inferred. This deviates from the assessment of the company, which allocated the outcome "health status" (EQ-5D VAS) to the outcome category "serious/severe symptoms/late complications" on the basis of a comparison of the study values at the start of the study with values in the average German population.

The outcome "pain" (VAS) was also allocated to the outcome category "non-serious/non-severe symptoms/late complications". The company provided no data that would justify the allocation of the values achieved for pain (VAS) in the relevant subpopulation of the JADV study to the outcome category "serious/severe symptoms/late complications". This deviates from the assessment of the company, which allocated the outcome "pain" to the outcome category "serious/severe symptoms/late complications" because of its importance in the present therapeutic indication.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 18).

Table 18: Extent of added benefit at outcome level: baricitinib + MTX vs. adalimumab + MTX (research question 2)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**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: 0.8% vs. 0.7% Peto OR: 1.25 [0.12; 12.87]; p = 0.919	Lesser benefit/added benefit not proven
Morbidity		
Remission (SDAI ≤ 3.3)	Proportion: 22.2% vs. 19.6% RR: 1.16 [0.78; 1.71]; p = 0.464	Lesser benefit/added benefit not proven
Low disease activity (DAS28-hsCRP ≤ 3.2)	Proportion: 57.2% vs. 49.7% RR: 1.14 [0.95; 1.38]; p = 0.161	Lesser benefit/added benefit not proven
Tender joint count[c]	Mean: -10.7 vs. -9.8 LSMD: -0.8 [-2.0; 0.4]; p = 0.184	Lesser benefit/added benefit not proven
Swollen joint count[c]	Mean: -8.2 vs. -7.9 LSMD: -0.8 [-1.7; 0.2]; p = 0.117	Lesser benefit/added benefit not proven
Pain (VAS) Sex		
Male	LSM: -42.28 vs. -26.53 LSMD: -15.75 [-24.26; -7.25]; p < 0.001 Hedges' g: -0.69 [-1.08; -0.30][d] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
Female	LSM: -33.90 vs. -34.20 LSMD: 0.30 [-5.72; 6.31]; p = 0.923	Lesser benefit/added benefit not proven
Disease activity (VAS) Sex		
Male	LSM: -43.36 vs. -28.67 LSMD: -14.69 [-23.39; -5.99]; p = 0.001 Hedges' g: -0.63 [-1.02; -0.25][d] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
Female	LSM: -34.02 vs. -31.72 LSMD: -2.30 [-8.07; 3.46]; p = 0.432	Lesser benefit/added benefit not proven

(continued)

Table 18: Extent of added benefit at outcome level: baricitinib + MTX vs. adalimumab + MTX (research question 2) (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Baricitinib + MTX vs. adalimumab + MTX** **Proportion of patients with event or change** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Morbidity		
Health status (EQ-5D VAS) Age		
< 65 years	LSM: 22.17 vs. 11.42 LSMD: 10.75 [5.21; 16.29]; p < 0.001 Hedges' g: 0.44 [0.21; 0.68][d] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
≥ 65 years	LSM: 13.22 vs. 16.03 LSMD: -2.81 [-13.26; 7.64]; p = 0.594	Lesser benefit/added benefit not proven
Morning stiffness[e]	Median: -40.0 vs. -15.0 Median of the differences: -17.0 [-50.0; 0.0]; p = 0.083	Lesser benefit/added benefit not proven
Fatigue (FACIT-F)	No usable data[f]	Lesser benefit/added benefit not proven
Physical functioning (HAQ-DI[g])	Proportion: 67.1% vs. 58.8% RR: 1.11 [0.95; 1.29]; p = 0.180	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36v2 acute, physical component summary[h]	Proportion: 64.2% vs. 53.6% RR: 1.16 [0.98; 1.38]; p = 0.086	Lesser benefit/added benefit not proven
SF-36v2 acute, mental component summary[h]	Proportion: 37.0% vs. 28.8% RR: 1.28 [0.96; 1.72]; p = 0.098	Lesser benefit/added benefit not proven
Side effects		
SAEs	Proportion: 8.6% vs. 2.6% RR: 3.31 [1.16; 9.45] RR[i]: 0.30 [0.11; 0.86]; p = 0.016 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Discontinuation due to AEs	Proportion: 5.8% vs. 4.6% RR: 1.26 [0.52; 3.05]; p = 0.653	Greater/lesser harm not proven
Infections	Proportion: 41.2% vs. 37.3% RR: 1.10 [0.86; 1.43]; p = 0.573	Greater/lesser harm not proven
serious infections	Proportion: 2.1% vs. 1.3% RR: 1.57 [0.31; 8.01]; p = 0.653	Greater/lesser harm not proven

(continued)

Table 18: Extent of added benefit at outcome level: baricitinib + MTX vs. adalimumab + MTX (research question 2) (continued)

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: Based on 28 joints.
d: 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.
e: Patients for whom a value of the duration in minutes recorded with an ePRO tablet is available at the start of the study.
f: The company presented no analyses for the relevant subpopulation for this outcome.
g: Patients with improvement by ≥ 0.22 points.
h: Patients with improvement by ≥ 5 points.
i: Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

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; Peto OR: Peto odds ratio; 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

2.5.3.2 Overall conclusion on the added benefit (research question 2)

Table 19 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 19: Positive and negative effects from the assessment of baricitinib + MTX in comparison with adalimumab + MTX (research question 2)

Positive effects	**Negative effects**
Non-serious/non-severe symptoms/late complications ▪ Pain (VAS) ▫ Sex: male hint of an added benefit – extent: "non-quantifiable" ▪ Disease activity (VAS) ▫ Sex: male hint of an added benefit – extent: "non-quantifiable" ▪ Health status (EQ-5D VAS) ▫ Age: < 65 years hint of an added benefit – extent: "non-quantifiable"	Serious/severe side effects ▪ SAEs ▫ hint of greater harm – extent: "considerable"
EQ-5D: European Quality of Life-5 Dimensions; MTX: methotrexate; SAE: serious adverse event; VAS: visual analogue scale	

In the overall assessment, there are positive and negative effects of equal certainty of results ("hint"). On the negative side, there is greater harm with the extent "considerable" in the category "serious/severe side effects" (SAEs). This is accompanied on the side of positive effects by an added benefit with the extent "non-quantifiable" in the category "non-

serious/non-severe symptoms/late complications" for men (pain [VAS] and disease activity [VAS]) and for patients < 65 years (health status [EQ-5D VAS]). For the positive effects, the 95% CI of Hedges' g, which was used for assessing the relevance of the effects, was not markedly outside the range that is certainly irrelevant. Hence the effects in the respective subgroups (men and patients < 65 years) did not outweigh the greater harm with the extent "considerable".

In summary, there is a hint of lesser benefit of baricitinib in comparison with adalimumab for patients with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with 1 cDMARD (including MTX) and with poor prognostic factors.

The result of the assessment of the added benefit of baricitinib in comparison with the ACT for patients with inadequate response to prior treatment with 1 cDMARD (including MTX) and with poor prognostic factors is summarized in Table 20.

Table 20: Baricitinib – probability and extent of added benefit (research question 2)

Therapeutic indication	**Appropriate comparator therapy[a]**	**Probability and extent of added benefit**
Patients with poor prognostic factors[b] who have responded inadequately to prior treatment with 1 disease-modifying antirheumatic drug (conventional DMARDs, including MTX)[c]	bDMARD in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in MTX intolerance	Hint of lesser benefit

a: Presentation of the appropriate comparator therapy specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: Poor prognostic factors: detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.
c: According to the SPC, baricitinib is also approved for patients who have not tolerated prior treatment with a DMARD [5]. The relevant subpopulation of the included study for the assessment of the added benefit (only patients who have shown inadequate response to MTX) therefore does not completely cover the therapeutic indication. It remains unclear whether the observed effects can be transferred to patients who have not tolerated prior treatment with a DMARD.
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DAS: Disease Activity Score; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate; SPC: Summary of Product Characteristics

This deviates from the approach of the company, which jointly derived an indication of a minor added benefit for patients of research questions 2 and 3 on the basis of the results of the mITT population.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG.

2.5.4 List of included studies (research question 2)

Eli Lilly. A study in moderate to severe rheumatoid arthritis (RA-BEAM): full text view [online]. In: ClinicalTrials.gov. 13.05.2016 [Accessed: 21.04.2017]. URL: https://ClinicalTrials.gov/show/NCT01710358.

Eli Lilly. A randomized, double-blind, placebo- and active controlled, phase 3 study evaluating the efficacy and safety of baricitinib in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate therapy [online]. In: EU Clinical Trials Register. [Accessed: 21.04.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-002322-73.

Eli Lilly. A randomized, double-blind, placebo- and active controlled, phase 3 study evaluating the efficacy and safety of baricitinib in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate therapy: clinical trial result [online]. In: EU Clinical Trials Register. 26.03.2017 [Accessed: 21.04.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-002322-73/results.

Eli Lilly. A randomized, double-blind, placebo- and active-controlled, phase 3 study evaluating the efficacy and safety of baricitinib in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate therapy: study I4V-MC-JADV; clinical protocol [unpublished]. 2013.

Eli Lilly. A randomized, double-blind, placebo- and active-controlled, phase 3 study evaluating the efficacy and safety of baricitinib in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate therapy: study I4V-MC-JADV; statistical analysis plan [unpublished]. 2015.

Eli Lilly. A randomized, double-blind, placebo- and active-controlled, phase 3 study evaluating the efficacy and safety of baricitinib in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate therapy: study I4V-MC-JADV; clinical study report [unpublished]. 2015.

Eli Lilly. A randomized, double-blind, placebo- and active-controlled, phase 3 study evaluating the efficacy and safety of baricitinib in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate therapy: study I4V-MC-JADV; Zusatzanalysen [unpublished]. 2017.

Taylor PC, Keystone EC, Van der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med 2017; 376(7): 652-662.

2.6 Research question 3: patients with inadequate response to pretreatment with several conventional DMARDs

2.6.1 Study characteristics (research question 3)

The study used for the benefit assessment with the subpopulation relevant for the present research question is described in Table 21.

Table 21: Characteristics of the study included – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 3)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
JADV	RCT, double-blind, parallel	Adult patients with moderate to severe active rheumatoid arthritis ▪ who have shown inadequate response to MTX ▪ who have not received prior treatment with bDMARDs ▪ who were treated with MTX for at least 12 weeks before study inclusion, of which at least 8 weeks before study inclusion with an oral dose of 7.5 to 25 mg/week (or equivalent injectable dose) ▪ whose last CRP or hsCRP value – if available – was ≥6 mg/L ▪ whose eGFR was ≥ 40 mL/min/1.73 m² Patients receiving corticosteroids at a dose of > 10 mg/day prednisone or equivalent were excluded.	Baricitinib + MTX[b] (N = 488)[c] adalimumab + MTX[d] (N = 330) placebo + MTX[e] (N = 489)[c, f] Relevant subpopulation thereof[g]: baricitinib + MTX (n = 170) adalimumab + MTX (n = 124)	Screening: 3 to 42 days before randomization Treatment: 52 weeks[h] Follow-up (for patients not participating in the JADY extension study): 28 days	335 study centres in Argentina, Belgium, Canada, China, Croatia, Czech Republic, France, Germany, Greece, Great Britain, Hungary, Japan, Latvia, Lithuania, Mexico, Netherlands, Poland, Portugal, Romania, Russia, Slovak Republic, Slovenia, Switzerland, South Africa, South Korea, Spain, Taiwan, United States of America 10/2012–9/2015	Primary: ▪ proportion of patients with ACR20 from the start of the study until week 12 in comparison with placebo Secondary: ▪ Morbidity ▪ health-related quality of life ▪ AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: 74 patients in this arm were receiving at least 1 further cDMARD at the start of the study.
c: 1 patient in this arm was not treated.
d: 53 patients in this arm were receiving at least 1 further cDMARD at the start of the study.
e: 89 patients in this arm were receiving at least 1 further cDMARD at the start of the study.
f: The arm is not relevant for the assessment and is not shown in the next tables.
g: Patients who have responded inadequately to prior treatment with several cDMARDs.
h: Patients allocated to placebo + MTX were switched to baricitinib + MTX at week 24.

ACR20: 20% improvement in American College of Rheumatology criteria; AE: adverse event; bDMARD: biologic disease-modifying antirheumatic drug; cDMARD: conventional disease-modifying antirheumatic drug; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; hsCRP: high-sensitivity C-reactive protein; MTX: methotrexate; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

The characteristics of the JADV study, including the characteristics of the interventions (see Table 8), are described in Section 2.5.1.

Relevant subpopulation for research question 3

For research question 3, the subpopulation of patients in the JADV study with inadequate response to prior treatment with several cDMARDs was relevant. In addition, the patients of the relevant subpopulation were not allowed to have been treated with several cDMARDs during the study because, according to the European Public Assessment Report (EPAR), baricitinib should not be combined with other DMARDs than MTX [6]. The relevant subpopulation comprised 170 patients in the intervention arm and 124 patients in the comparator arm.

Patient characteristics

Table 22 and Table 23 show the characteristics of the patients in the relevant subpopulation of the study included.

Table 22: Characteristics of the relevant subpopulation – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 3)

Study Characteristics Category	**Baricitinib + MTX**	**Adalimumab + MTX**
JADV	N[a] = 170	N[a] = 124
Age [years], mean (SD)	52.5 (11.7)	53.0 (12.4)
Sex [F/M], %	81.2/18.8	83.9/16.1
Region, n (%)		
Central and South America and Mexico	38 (22.4)	32 (25.8)
Eastern Europe	37 (21.8)	30 (24.2)
Japan	48 (28.2)	29 (23.4)
USA and Canada	6 (3.5)	2 (1.6)
Western Europe	6 (3.5)	8 (6.5)
Asia (without Japan)	16 (9.4)	9 (7.3)
Rest of the world	19 (11.2)	14 (11.3)
Disease duration: time between first diagnosis and randomization [years], mean (SD)	10.4 (8.0)	10.2 (7.9)
Functional status [HAQ-DI], mean (SD)	1.41 (0.64)	1.60 (0.72)
Tender joint count[b], mean (SD)	21.0 (11.5)	21.4 (11.8)
Swollen joint count[c], mean (SD)	15.0 (8.3)	14.2 (6.3)
Rheumatoid factor status, n (%)		
Positive	153 (90.0)	119 (96.0)
Negative	17 (10.0)	5 (4.0)
ACPA status, n (%)		
Positive	153 (90.0)	112 (90.3)
Negative	14 (8.2)	10 (8.1)
Undetermined	3 (1.8)	2 (1.6)
DAS28-hsCRP, n (%)		
≤ 3.2	2 (1.2)	0 (0)
> 3.2 to ≤ 5.1	51 (30.0)	33 (26.6)
> 5.1	117 (68.8)	91 (73.4)
Renal function [eGFR], n (%)		
< 60 mL/min/1.73 m^2	6 (3.5)	8 (6.5)
≥ 60 mL/min/1.73 m^2	164 (96.5)	116 (93.5)
Bone/joint erosion score[d], mean (SD)	27.7 (27.9)	28.5 (31.6)
Joint space narrowing score[e] mean (SD)	19.4 (22.5)	20.3 (25.1)
Patients with adjustment of therapy[f], n (%)	16 (9.4)	17 (13.7)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	20 (11.8)[g]	13 (10.5)[g]

(continued)

Table 22: Characteristics of the relevant subpopulation – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 3) (continued)

a: Number of analysed patients in relevant subpopulation. 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

Table 23: Pretreatment and concomitant treatment of the relevant subpopulation – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 3)

Study Characteristics Category	**Baricitinib + MTX**	**Adalimumab + MTX**
JADV	N[a] = 170	N[a] = 124
Pretreatment: number of cDMARDs, n (%)		
1	0 (0)	0 (0)
2 (including MTX)	93 (54.7)	77 (62.1)
≥ 3 (including MTX)	77 (45.3)	47 (37.9)
Pretreatment: type of cDMARDs (except MTX)	ND	ND
Concomitant treatment at the start of the study		
MTX dose [mg/week], mean (SD)	14.8 (4.9)	14.6 (4.2)
Corticosteroids		
n (%)	101 (59.4)	75 (60.5)
Dose [mg/day], mean (SD)[b]	5.5 (2.7)	5.8 (2.2)

a: Number of analysed patients in relevant subpopulation.
b: Analysis of patients with corticosteroid treatment at the start of the study.
cDMARD: conventional disease-modifying antirheumatic drug; 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

Overall, the patient characteristics between the arms of the JADV study in the relevant subpopulation were balanced. The mean age of the patients was 53 years. Markedly more women (81 to 84%) than men were included in both arms, reflecting the higher prevalence of rheumatoid arthritis in women [3].

A marked majority of patients was seropositive (positive rheumatoid factor and/or positive ACPA serostatus). Additional analyses in Module 5 showed that 163 (95.9%) of the patients in the intervention arm and 121 (97.6%) of the patients in the comparator arm were

seropositive. All but 2 patients had moderate to high disease activity (DAS28-hsCRP > 3.2). The distribution of these disease characteristics shows that patients in both study arms were patients with poor prognostic factors.

From week 16, 9.4% of the patients in the intervention arm and 13.7% of the patients in the comparator arm received adjustment of therapy due to inadequate response (rescue therapy). These adjustments of therapy were taken into account in the assessment of the risk of bias. There was no information on treatment discontinuations for the relevant subpopulation.

Risk of bias at study level

The risk of bias at study level for the JADV study was rated as low (see Table 11 in Section 2.5.1). This concurs with the company's assessment.

2.6.2 Results on added benefit (research question 3)

2.6.2.1 Outcomes included (research question 3)

The patient-relevant outcomes listed for research question 2 were also to be included in the assessment for research question 3 (see Section 2.5.2.1). For both research questions, the choice of patient-relevant outcomes deviates from that of the company in the same way (see Section 2.9.2.4.3 of the full dossier assessment).

The data availability at outcome level for research question 3 and research question 2 was identical (see Table 12 in Section 2.5.2.1).

2.6.2.2 Risk of bias (research question 3)

Table 24 shows the risk of bias for the relevant outcomes.

Table 24: Risk of bias at study and outcome level – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 3)

Study	Study level	Outcomes															
		All-cause mortality	Remission (SDAI ≤ 3.3)	Low disease activity (DAS28-hsCRP ≤ 3.2)	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]	-[g]	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 (18.8%) and in the comparator arm (21.8%).
g: The company presented no analyses for the relevant subpopulation for this outcome.

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 for research questions 2 and 3 was identical for all outcomes (see Section 2.5.2.2). For those outcomes for which the proportions of values imputed using LOCF or NRI for research question 3 deviated marginally from research question 2 in the intervention arm (18.8%) and in the comparator arm (21.8%), this deviation did not change the assessment of the risk of bias in comparison with research question 2.

For research questions 2 and 3, the assessments of the risk of bias at outcome level deviated in the same way from those of the company, which rated the risk of bias as low for all outcomes, except for the outcomes "fatigue" and "serious infections", which were not used by the company.

Detailed reasons for the assessment of the risk of bias can be found in Section 2.9.2.4.2 of the full dossier assessment.

2.6.2.3 Results (research question 3)

Table 25 and Table 26 summarize the results of the comparison of baricitinib + MTX with adalimumab + MTX in patients with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with several cDMARDs (including MTX). Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 25: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 3)

Study Outcome category Outcome	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)					
Mortality					
All-cause mortality	170	0 (0)	124	0 (0)	NC
Morbidity					
Remission (SDAI ≤ 3.3)	170	40 (23.5)	124	20 (16.1)	1.46 [0.90; 2.36]; 0.125[a]
Low disease activity (DAS28-hsCRP ≤ 3.2)	170	93 (54.7)	124	64 (51.6)	1.05 [0.85; 1.31]; 0.640[a]
Physical functioning (HAQ-DI[b])	170	116 (68.2)	124	78 (62.9)	1.08 [0.91; 1.29]; 0.371[a]
Health-related quality of life					
SF-36v2 acute					
Physical component summary[c]	170	95 (55.9)	124	68 (54.8)	1.03 [0.83; 1.26]; 0.811[a]
Mental component summary[c]	170	50 (29.4)	124	45 (36.3)	0.87 [0.63; 1.19]; 0.374[a]
Side effects					
AEs (supplementary information)	170	145 (85.3)	124	101 (81.5)	-
SAEs	170	12 (7.1)	124	5 (4.0)	1.75 [0.63; 4.84]; 0.344[d]
Discontinuation due to AEs[e]	170	14 (8.2)	124	4 (3.2)	2.55 [0.86; 7.57]; 0.078[d]
Infections[f]	170	98 (57.7)	124	63 (50.8)	1.13 [0.91; 1.41]; 0.343[d]
Serious infections[g]	170	5 (2.9)[h]	124	1 (0.8)[h]	3.65 [0.43; 30.83][i]; 0.221[d]

(continued)

Table 25: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 3) (continued)

a: According to the company calculated using a logistic regression model; missing data were imputed using NRI.
b: Patients with improvement by ≥ 0.22 points.
c: Patients with improvement by ≥ 5 points.
d: Institute's calculation, unconditional exact test (CSZ method according to [4]).
e: Treatment discontinuation due to AEs.
f: AEs of the SOC "infections and infestations".
g: SAEs of the SOC "infections and infestations".
h: Institute's calculation.
i: Institute's calculation of effect and CI (asymptotic).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; DAS: Disease Activity Score; HAQ-DI: Health Assessment Questionnaire-Disability Index; hsCRP: high-sensitivity C-reactive protein; MTX: methotrexate; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculated; NRI: non-responder imputation; 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 26: Results (morbidity, continuous) – RCT, direct comparison: baricitinib + MTX vs. adalimumab + MTX (research question 3)

Study Outcome category Outcome	Baricitinib + MTX			Adalimumab + MTX			Baricitinib + MTX vs. adalimumab + MTX
	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[c]
JADV (week 52)							
Morbidity							
Tender joint count[d]	170	13.0 (6.3)	-9.1 (6.4)	123	13.0 (6.6)	-8.7 (6.8)	-0.6 [-1.8; 0.6]; 0.325
Swollen joint count[d]	170	11.0 (4.8)	-8.1 (5.7)	123	10.6 (5.1)	-7.2 (5.4)	-0.6 [-1.6; 0.4]; 0.270
Pain (VAS)	170	58.5 (21.4)	-37.6 (27.5)	123	58.9 (22.0)	-32.0 (27.4)	-5.9 [-11.0; -0.8]; 0.023 Hedges' g: -0.27 [-0.50; -0.04][e]
Disease activity (VAS)	170	61.1 (20.9)	-38.3 (26.5)	123	62.2 (20.5)	-34.2 (28.0)	-5.2 [-10.4; -0.1]; 0.046 Hedges' g: -0.23 [-0.47; -0.00][e]
Health status (EQ-5D VAS)	169	51.0 (20.3)	20.9 (27.7)	121	51.7 (21.4)	15.5 (29.3)	5.6 [0.1; 11.2]; 0.046 Hedges' g: 0.24 [0.00; 0.47][e]
Morning stiffness[f]	98	Median: 60.0	Median: -60.0 95% CI: [-60.0; -30.0]	79	Median: 60.0	Median: -30.0 95% CI: [-60.0; -19.0]	Median of the differences: -10.0 [-40.0; 9.0][g]; 0.240[h]
Fatigue (FACIT-F)	No usable data[i]						

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, unless stated otherwise.
d: Based on 28 joints.
e: Institute's calculation based on the LSMD and the SE from the ANCOVA.
f: Patients for whom a value of the duration in minutes recorded with an ePRO tablet is available at the start of the study; the median-based analyses are used because these were primarily planned.
g: Hodges-Lehmann estimator.
h: Wilcoxon rank sum test.
i: The company presented no analyses for the relevant subpopulation for this outcome.

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 added benefit can be derived for the outcome "remission". For all other outcomes, at most hints of an added benefit can be derived due to the high risk of bias (see Section 2.6.2.2 and Section 2.9.2.4.2 of the full dossier assessment). This deviates from the assessment of the company, which rated the risk of bias as low for all outcomes and derived at most indications of an added benefit for all outcomes.

The derivation of the added benefit was based on the results for the relevant subpopulation. This deviates from the approach of the company, which based its derivation of the added benefit for all outcomes on the results of the mITT population (see Section 2.9.2.8.2 of the full dossier assessment).

Mortality

All-cause mortality

No deaths occurred in any of the 2 treatment groups until treatment week 52. This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for the outcome "mortality"; an added benefit is therefore not proven.

This concurs with the assessment of the company, which analysed this outcome in the framework of SAEs, using the designation "deaths", however.

Morbidity

Remission

No statistically significant difference between the treatment groups was shown for the outcome "remission" (SDAI $\leq$ 3.3). This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company, which also derived no added benefit for the outcome "remission" (operationalized using the achievement of both an SDAI $\leq$ 3.3 and a DAS28-hsCRP < 2.6).

For the present benefit assessment, the definition based on the CDAI ($\leq$ 2.8) and the Boolean definition (tender joint count $\leq$ 1 and swollen joint count $\leq$ 1 and hsCRP $\leq$ 1 mg/dL and disease activity [VAS from 0 to 10 cm] $\leq$ 1 cm) were also to be considered for the outcome "remission" according to the ACR/EULAR. The corresponding analyses had been planned in the JADV study. The company, however, provided no analyses for the relevant subpopulation for these definitions (see also Section 2.9.2.4.3 of the full dossier assessment). It can therefore not be evaluated for the relevant subpopulation whether the results for the outcome "remission" largely depend on the definition used.

Low disease activity (DAS28-hsCRP ≤ 3.2)

No statistically significant difference between the treatment groups was shown for the outcome "low disease activity" (DAS28-hsCRP ≤ 3.2). This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company, which also derived no added benefit for the outcome "low disease activity" (operationalized using the achievement of both a DAS28-hsCRP < 3.2 and a CDAI ≤ 10).

Tender joint count

For the outcome "tender joint count", no statistically significant difference between the treatment groups was shown for the mean change. This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which claimed an indication of an added benefit on the basis of the mITT population of the JADV study.

Swollen joint count

For the outcome "swollen joint count", no statistically significant difference between the treatment groups was shown for the mean change. This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which claimed an indication of an added benefit on the basis of the mITT population of the JADV study.

Pain (VAS)

For the outcome "pain" (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 added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which additionally included analyses of the proportions of patients with a VAS improvement by both ≥ 10 mm and ≥ 20 mm in its assessment. These response criteria were considered to be unvalidated (see Section 2.9.2.4.3 of the full dossier assessment). On the basis of the responder analyses and on the analysis of the mean change in the mITT population of the JADV study, the company claimed an indication of an added benefit.

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 added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company, which overall also derived no added benefit.

Health status (EQ-5D VAS)

For the outcome "health status" (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 added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which additionally included analyses of the proportions of patients with a VAS improvement by ≥ 10 mm in its assessment. This response criterion was considered to be unvalidated (see Section 2.9.2.4.3 of the full dossier assessment). On the basis of the responder analyses and on the analysis of the mean change in the mITT population of the JADV study, the company claimed an indication of an added benefit.

Morning stiffness

No statistically significant difference between the treatment groups was shown for the outcome "morning stiffness" for the median of the differences (primarily planned type of analysis). This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which – deviating from the primarily planned type of analysis for this outcome – claimed an indication of an added benefit on the basis of the mITT population of the JADV study by analysing the mean change.

Fatigue (FACIT-F)

The company presented no analyses for the relevant subpopulation for the outcome "fatigue" (FACIT-F). This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This deviates from the approach of the company insofar as the company did not use the outcome "fatigue" (FACIT-F) in its assessment.

Physical functioning (HAQ-DI)

No statistically significant difference between the treatment groups was shown for the outcome "physical functioning" (improvement in HAQ-DI by ≥ 0.22 points). This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which claimed an indication of an added benefit for the HAQ-DI on the basis of the mITT population of the JADV study by analysing both the proportions of patients with an improvement by ≥ 0.22 points and the mean change.

Health-related quality of life

SF-36v2 acute – physical component summary

No statistically significant difference between the treatment groups was shown for the physical component summary of the SF-36v2 acute (improvement by ≥ 5 points). This resulted in no hint of an added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which claimed an indication of an added benefit on the basis of the mITT population of the JADV study analysing both the proportions of patients with an improvement by ≥ 5 points and the mean change.

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 added benefit of baricitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This deviates from the approach of the company, which additionally included the analysis of the mean change in its assessment. The company then derived no added benefit on the basis of these analyses, however.

Side effects

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs". Hence for this outcome, there was no hint of greater or lesser harm from baricitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven.

This deviates from the approach of the company, which derived an indication of greater risk of harm on the basis of the mITT population of the JADV study.

Discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs" (treatment discontinuation due to AEs). Hence for this outcome, there was no hint of greater or lesser harm from baricitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Infections

No statistically significant difference between the treatment groups was shown for the outcome "infections" (AEs of the SOC "infections and infestations"). Hence for this outcome, there was no hint of greater or lesser harm from baricitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Serious infections

No statistically significant difference between the treatment groups was shown for the outcome "serious infections" (SAEs of the SOC "infections and infestations"). Hence for this outcome, there was no hint of greater or lesser harm from baricitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven.

This deviates from the approach of the company insofar as the company did not use the outcome "serious infections" in its assessment.

Further specific adverse events

The dossier contained no usable data for the relevant subpopulation for the choice of further specific AEs (see Section 2.9.2.4.3 of the full dossier assessment).

2.6.2.4 Subgroups and other effect modifiers (research question 3)

The subgroup characteristics considered relevant for the present benefit assessment and the corresponding subgroup analyses presented by the company were identical for research questions 2 (see Section 2.5.2.4) and 3 (see also Section 2.9.2.4.3 of the full dossier assessment).

For research question 3, there were no subgroup results with at least an indication of an interaction between treatment and subgroup characteristic and a statistically significant and relevant effect in at least 1 subgroup.

The approach of the company deviates insofar as it presented results of individual subgroups for each outcome for the relevant subpopulation only if there was proof of an interaction between treatment and subgroup characteristic. The company derived no separate added

benefit by subgroups (see Section 2.9.2.4.3 of the full dossier assessment, subgroup characteristics and other effect modifiers).

2.6.3 Probability and extent of added benefit (research question 3)

The derivation of probability and extent of added benefit is presented below at outcome level for patients with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with several cDMARDs (including MTX), taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG.

2.6.3.1 Assessment of added benefit at outcome level (research question 3)

The data presented in Section 2.6.2 resulted in no statistically significant and relevant effects of baricitinib + MTX in comparison with adalimumab + MTX in patients with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with several cDMARDs (including MTX). The extent of the respective added benefit at outcome level was estimated from these results (see Table 27).

Table 27: Extent of added benefit at outcome level: baricitinib + MTX vs. adalimumab + MTX (research question 3)

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% vs. 0% -	Lesser benefit/added benefit not proven
Morbidity		
Remission (SDAI ≤ 3.3)	Proportion: 23.5% vs. 16.1% RR: 1.46 [0.90; 2.36]; p = 0.125	Lesser benefit/added benefit not proven
Low disease activity (DAS28-hsCRP ≤ 3.2)	Proportion: 54.7% vs. 51.6% RR: 1.05 [0.85; 1.31]; p = 0.640	Lesser benefit/added benefit not proven
Tender joint count[c]	Mean: -9.1 vs. -8.7 LSMD: -0.6 [-1.8; 0.6]; p = 0.325	Lesser benefit/added benefit not proven
Swollen joint count[c]	Mean: -8.1 vs. -7.2 LSMD: -0.6 [-1.6; 0.4]; p = 0.270	Lesser benefit/added benefit not proven
Pain (VAS)	Mean: -37.6 vs. -32.0 LSMD: -5.9 [-11.0; -0.8]; p = 0.023 Hedges' g: -0.27 [-0.50; -0.04][d]	Lesser benefit/added benefit not proven
Disease activity (VAS)	Mean: -38.3 vs. -34.2 LSMD: -5.2 [-10.4; -0.1]; p = 0.046 Hedges' g: -0.23 [-0.47; -0.00][d]	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	Mean: 20.9 vs. 15.5 LSMD: 5.6 [0.1; 11.2]; p = 0.046 Hedges' g: 0.24 [0.00; 0.47][d]	Lesser benefit/added benefit not proven
Morning stiffness[e]	Median: -60.0 vs. -30.0 Median of the differences: -10.0 [-40.0; 9.0]; p = 0.240	Lesser benefit/added benefit not proven
Fatigue (FACIT-F)	No usable data[f]	Lesser benefit/added benefit not proven
Physical functioning (HAQ-DI[g])	Proportion: 68.2% vs. 62.9% RR: 1.08 [0.91; 1.29]; p = 0.371	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36v2 acute, physical component summary[h]	Proportion: 55.9% vs. 54.8% RR: 1.03 [0.83; 1.26]; p = 0.811	Lesser benefit/added benefit not proven
SF-36v2 acute, mental component summary[h]	Proportion: 29.4% vs. 36.3% RR: 0.87 [0.63; 1.19]; p = 0.374	Lesser benefit/added benefit not proven

(continued)

Table 27: Extent of added benefit at outcome level: baricitinib + MTX vs. adalimumab + MTX (research question 3) (continued)

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]
Side effects		
SAEs	Proportion: 7.1% vs. 4.0% RR: 1.75 [0.63; 4.84]; p = 0.344	Greater/lesser harm not proven
Discontinuation due to AEs	Proportion: 8.2% vs. 3.2% RR: 2.55 [0.86; 7.57]; p = 0.078	Greater/lesser harm not proven
Infections	Proportion: 57.7% vs. 50.8% RR: 1.13 [0.91; 1.41]; p = 0.343	Greater/lesser harm not proven
Serious infections	Proportion: 2.9% vs. 0.8% RR: 3.65 [0.43; 30.83]; p = 0.221	Greater/lesser harm 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: Based on 28 joints.
d: 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.
e: Patients for whom a value of the duration in minutes recorded with an ePRO tablet is available at the start of the study.
f: The company presented no analyses for the relevant subpopulation for this outcome.
g: Patients with improvement by ≥ 0.22 points.
h: 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

2.6.3.2 Overall conclusion on the added benefit (research question 3)

Table 28 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 28: Positive and negative effects from the assessment of baricitinib + MTX in comparison with adalimumab + MTX (research question 3)

Positive effects	**Negative effects**
–	–

MTX: methotrexate

Overall, there are neither positive nor negative effects. This resulted in no hint of an added benefit of baricitinib in comparison with the ACT for patients with moderate to severe active rheumatoid arthritis who have responded inadequately to prior treatment with several cDMARDs (including MTX). An added benefit is therefore not proven.

This deviates from the approach of the company, which jointly derived an indication of a minor added benefit for patients of research questions 2 and 3 on the basis of the results of the mITT population.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG.

2.6.4 List of included studies (research question 3)

The list of included studies was identical for research questions 2 and 3 (see Section 2.5.4).

2.7 Research question 4: patients with inadequate response to pretreatment with 1 or several bDMARDs

2.7.1 Results on added benefit (research question 4)

The company presented no data for the assessment of the added benefit of baricitinib in comparison with the ACT for patients who have responded inadequately to prior treatment with 1 or several bDMARDs. This resulted in no hint of an added benefit of baricitinib in comparison with the ACT. An added benefit is therefore not proven.

2.7.2 Probability and extent of added benefit (research question 4)

The company presented no data for the assessment of the added benefit of baricitinib in patients who have responded inadequately to prior treatment with 1 or several bDMARDs. An added benefit of baricitinib in comparison with the ACT is therefore not proven for these patients.

This concurs with the assessment of the company, which claimed no added benefit for patients who have responded inadequately to prior treatment with 1 or several bDMARDs.

2.7.3 List of included studies (research question 4)

Not applicable as the company presented no relevant data for research question 4 for the benefit assessment.

2.8 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of baricitinib in comparison with the ACT is summarized in Table 29.

Table 29: Baricitinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
1	Patients without poor prognostic factors[c] who have responded inadequately to prior treatment with 1 disease-modifying antirheumatic drug (conventional DMARDs, including MTX)	Alternative conventional DMARDs if suitable (e.g. MTX, leflunomide) as monotherapy or combination therapy	Added benefit not proven
2	Patients with poor prognostic factors[c] who have responded inadequately to prior treatment with 1 disease-modifying antirheumatic drug (conventional DMARDs, including MTX)[d]	bDMARD in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in MTX intolerance	Hint of lesser benefit
3	Patients who have responded inadequately to prior treatment with several disease-modifying antirheumatic drugs (conventional DMARDs, including MTX)	bDMARD in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in MTX intolerance	Added benefit not proven
4	Patients who have responded inadequately to prior treatment with 1 or several bDMARDs	Switching of bDMARD treatment (adalimumab or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab; in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in MTX intolerance; or in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on prior therapy Depending on prior therapy, switching the mechanism of action should be considered.	Added benefit not proven

(continued)

Table 29: Baricitinib – probability and extent of added benefit (continued)

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: After prior therapy with already 2 drugs of one class, continuation of treatment with the same drug class has to be justified based on the underlying medical rationale.
c: Poor prognostic factors: detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.
d: According to the SPC, baricitinib is also approved for patients who have not tolerated prior treatment with a DMARD [5]. The relevant subpopulation of the included study for the assessment of the added benefit (only patients who have shown inadequate response to MTX) therefore does not completely cover the therapeutic indication. It remains unclear whether the observed effects can be transferred to patients who have not tolerated prior treatment with a DMARD.
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DAS: Disease Activity Score; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate; SPC: Summary of Product Characteristics

No data for the assessment of the added benefit were available for patients with moderate to severe active rheumatoid arthritis without poor prognostic factors who have responded inadequately to prior treatment with 1 cDMARD (including MTX) (research question 1) and for patients who have responded inadequately to prior treatment with 1 or several bDMARDs (research question 4). An added benefit of baricitinib versus the ACT is therefore not proven for these patients. This concurs with the company's assessment.

There is a hint of lesser benefit of baricitinib in comparison with the ACT adalimumab for patients with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with 1 cDMARD (including MTX) and with poor prognostic factors (research question 2). An added benefit of baricitinib in comparison with the ACT is not proven for patients with moderate to severe active rheumatoid arthritis who have responded inadequately to prior treatment with several cDMARDs (including MTX) (research question 3). This deviates from the assessment of the company, which jointly derived an indication of a minor added benefit for patients with inadequate response to prior treatment with 1 or several cDMARDs (including) MTX and poor prognostic factors on the basis of the results of the mITT population.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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