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Upadacitinib (rheumatoid arthritis) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Upadacitinib (rheumatoide Arthritis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 17 June 2020). 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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List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ACR20	20% improvement in ACR criteria
ACT	appropriate comparator therapy
AE	adverse event
bDMARD	biologic DMARD
CCP	cyclic citrullinated peptide
CDAI	Clinical Disease Activity Index
CI	confidence interval
CMQ	Custom MedDRA Query
CRP	C-reactive protein
csDMARD	conventional synthetic DMARD
DAS	Disease Activity Score
DAS28	DAS based on 28 joints
DMARD	disease-modifying antirheumatic drug
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	US Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HAQ-DI	Health Assessment Questionnaire-Disability Index
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MTX	methotrexate
NRI	non-responder imputation
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drugs
RCT	randomized controlled trial
RLOCF	rescue last observation carried forward
RNRI	NRI after switch to rescue therapy

Abbreviation	Meaning
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)
SMD	standardized mean difference
SOC	System Organ Class
SPC	Summary of Product characteristics
tsDMARD	targeted synthetic DMARD
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 upadacitinib. 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 16 January 2020.

Research question

The aim of the present report is the assessment of the added benefit of upadacitinib as monotherapy or in combination with methotrexate (MTX) in comparison with the appropriate comparator therapy (ACT) in adult patients with moderate to severe active rheumatoid arthritis who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs).

The G-BA differentiated between 3 patient groups in its specification of the ACT in the approved therapeutic indication. This resulted in 3 research questions for the assessment; their therapeutic indications and ACTs are presented in Table 2.

Table 2: Research questions of the benefit assessment of upadacitinib

Research question	Subindication	ACT[a]
Adults with moderate to severe active rheumatoid arthritis		
1	Patients without poor prognostic factors[b] who have responded inadequately to, or who are intolerant to prior treatment with one csDMARD[c] (including MTX)	Alternative csDMARDs[c] if suitable (e.g. MTX, leflunomide) as monotherapy or combination therapy
2	Patients for whom a first therapy with bDMARDs or tsDMARDs is indicated[d]	bDMARDs or tsDMARDs (abatacept or **adalimumab** or baricitinib or certolizumab pegol or etanercept or golimumab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability)
3	Patients who have responded inadequately to, or who are intolerant to prior treatment with one or more bDMARDs and/or tsDMARDs	Switching of bDMARD or tsDMARD therapy (**abatacept** or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability; or, in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on prior therapy[e]

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. Poor prognostic factors: detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antigen 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. In the G-BA's specification of the ACT, csDMARDs are referred to as "classical DMARDs". The present benefit assessment uses the term "csDMARDs".
d. This comprises both patients with poor prognostic factors who have responded inadequately to, or who have not tolerated previous treatment with one csDMARD (including MTX), and patients who have responded inadequately to or have not tolerated previous treatment with several csDMARDs (including MTX).
e. Switching the mode of action should be considered depending on the prior therapy.

ACT: appropriate comparator therapy; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate; tsDMARD: targeted synthetic DMARD

For easier presentation and better readability, the present benefit assessment uses the following terms for the research questions in the running text:

- Research question 1: adult patients without poor prognostic factors and with inadequate response or intolerance to pretreatment with one conventional synthetic DMARD (csDMARD)
- Research question 2: adult patients for whom a first therapy with biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated
- Research question 3: adult patients with inadequate response or intolerance to pretreatment with one or more bDMARDs and/or tsDMARDs

Research questions 1, 2 and 3 of the present benefit assessment correspond to the patient groups a, b and c in the G-BA's specification of the ACT. From the treatment options presented, the company chose adalimumab for research question 2 and abatacept for research question 3.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data presented 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.

Research question 1: adult patients without poor prognostic factors and with inadequate response or intolerance to pretreatment with one csDMARD

For research question 1, no data were available for the benefit assessment of upadacitinib in comparison with the ACT. Thus, an added benefit of upadacitinib in comparison with the ACT is not proven for adult patients who have no poor prognostic factors and have responded inadequately to or have not tolerated previous treatment with one csDMARD.

Research question 2: adult patients for whom a first therapy with bDMARDs or tsDMARDs is indicated

Study pool and study characteristics

The study pool of the benefit assessment of upadacitinib in comparison with the ACT for research question 2 consisted of the RCT SELECT-COMPARE, which compared upadacitinib + MTX with adalimumab + MTX. The SELECT-COMPARE study is exclusively suitable to derive conclusions on the added benefit of upadacitinib for the combination therapy with MTX.

The SELECT-COMPARE study is a 3-arm, randomized, double-blind study on the comparison of upadacitinib with adalimumab and placebo, each in combination with MTX. The study included adult patients with moderate to severe active rheumatoid arthritis who have an inadequate response to MTX. The patients had to have received continuous treatment with MTX for ≥ 3 months and had to continue this therapy as concomitant treatment during the study.

A total of 1629 patients were randomly allocated in a ratio of 2:1:2 to the 3 treatment arms of upadacitinib + MTX (N = 651), adalimumab + MTX (N = 327) and placebo + MTX (N = 651). Only the study arms of upadacitinib + MTX and adalimumab + MTX are relevant for the present benefit assessment.

Treatment with upadacitinib and adalimumab was in compliance with the recommendations of the respective Summaries of Product Characteristics (SPCs). The double-blind, randomized treatment phase was 48 weeks. Treatment of the patients is continued as open-label treatment in the subsequent, still ongoing extension phase.

For the European Medicines Agency (EMA), the primary outcome of the study was defined as the proportion of patients with a Disease Activity Score (DAS) based on 28 joints (DAS28) < 2.6; for the US Food and Drug Administration (FDA), it was defined as the proportion of patients with a 20% improvement in American College of Rheumatology (ACR) criteria (ACR20), each at week 12. Patient-relevant outcomes on morbidity, health-related quality of life and adverse events (AEs) were additionally recorded.

In the SELECT-COMPARE study, patients switched, in the framework of a rescue therapy, to the respective other treatment arm at predefined time points from week 14 if certain criteria for response to treatment were not met, while maintaining blinding. In addition, as of week 26, adjustments of concomitant medication according to local requirements were permitted.

Dates of analysis

Analyses for 3 time points are available for the ongoing SELECT-COMPARE study:

- analyses at week 26, based on the predefined data cut-off from 2 February 2018, after all randomized patients had reached week 26
- analyses at week 48, based on the data cut-off from 6 July 2018, after all randomized patients had completed the double-blind treatment phase (week 48)
- analyses at week 72, based on the data cut-off from 26 December 2018, after all randomized patients had reached week 72; thus the analyses also include data after unblinding of treatment

The analyses at week 26 were used in the present benefit assessment, as at week 48 almost half of the patients in the comparator arm had switched to upadacitinib + MTX as rescue therapy. At week 26, the proportion of patients with treatment switch in the comparator arm was about 1 quarter. The switch from adalimumab to upadacitinib, which was not yet to be considered a standard therapy at the time of approval, may be a potentially biasing factor for the results of the benefit assessment. In the present situation, the risk of bias was more pronounced at week 48 than at week 26 due to the notably higher proportion of patients with such a switch. Therefore, the analyses at week 26 were used for the present benefit present assessment.

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes was rated as low for the SELECT-COMPARE study. The outcome-specific risk of bias was rated as high for the results of all outcomes, with the exception of the outcome "clinical remission".

For morbidity and health-related quality of life outcomes, in case of statistically significant and, if applicable, clinically relevant results of the primary analysis in which patients with a treatment switch or discontinuation were included as non-responders or with their last observed values, sensitivity analyses were used in which values of patients with treatment switch were not imputed. If the results were consistent, the certainty of conclusions of the results was not downgraded despite the high risk of bias.

Results

Mortality

All-cause mortality

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome „all-cause mortality". This resulted in a hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX.

Morbidity

Clinical remission

The outcome "clinical remission" was operationalized using the Clinical Disease Activity Index (CDAI) ≤ 2.8, the Simplified Disease Activity Index (SDAI) ≤ 3.3, or the Boolean definition according to ACR/European League Against Rheumatism (EULAR). The assessment of clinical remission was primarily based on the CDAI ≤ 2.8.

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome „clinical remission" based on the CDAI ≤ 2.8. This resulted in an indication of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX. This effect was confirmed by the results of the operationalizations SDAI ≤ 3.3 and Boolean definition.

Low disease activity

The outcome "low disease activity" was operationalized as reaching the criteria of CDAI ≤ 10 and SDAI ≤ 11. The assessment of low disease activity was primarily based on the CDAI ≤ 10.

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome „low disease activity" based on the CDAI ≤ 10. Since the sensitivity analysis without imputation of patients with treatment switch confirmed this effect regarding statistical significance, there was an indication of an added benefit of upadacitinib + MTX versus adalimumab + MTX despite the high risk of bias. This effect was confirmed by the results of the SDAI ≤ 11.

Tender joints

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome „tender joints" based on the mean differences. The corresponding 95% confidence interval (CI) of the mean difference included a difference of < 1 joint. It can therefore not be inferred that the effect was relevant. This was confirmed in the sensitivity analysis. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

Swollen joints

For the outcome „swollen joints", no statistically significant difference between the treatment groups was shown based on the mean differences. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

Pain (visual analogue scale [VAS])

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome "pain (VAS)". The standardized mean difference (SMD) in the form of Hedges' g was considered to check the relevance of the result. However, the 95% CI of the SMD was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect was relevant. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

Patient assessment of disease activity (VAS)

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome "patient assessment of disease activity (VAS)". The SMD in the form of Hedges' g was considered to check the relevance of the result. However, the 95% CI was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect was relevant. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

Physical functioning (Health Assessment Questionnaire-Disability Index [HAQ-DI])

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome "physical functioning (HAQ-DI)". Since the sensitivity analysis did not confirm this effect regarding statistical significance, there was a hint of an added benefit of upadacitinib + MTX versus adalimumab + MTX due to the high risk of bias.

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

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome "fatigue (FACIT-Fatigue)". The extent of the effect was no more than marginal, however. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

Morning stiffness (severity [numeric rating scale, NRS], duration)

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome "severity (NRS) of morning stiffness". The SMD in the form of Hedges' g was considered to check the relevance of the result. However, the 95% CI of the SMD was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect was relevant. There was no statistically significant difference between the treatment groups for the duration of morning stiffness. This did not result in a hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX for the severity (NRS) or for the duration of morning stiffness; an added benefit is therefore not proven.

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

There was no statistically significant difference between the treatment groups for the outcome "health status (EQ-5D VAS)". This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

Health-related quality of life

Short Form (36) – version 2 Health Survey (SF-36v2) – Physical and Mental Component Summary

A statistically significant difference in favour of upadacitinib + MTX was shown for the Physical Component Summary of the SF-36v2. Since the sensitivity analysis did not confirm this effect regarding statistical significance, there was a hint of an added benefit of upadacitinib + MTX versus adalimumab + MTX due to the high risk of bias.

No statistically significant difference between the treatment groups was shown for the Mental Component Summary of the SF-36v2. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs), discontinuation due to AEs, infections, serious infections

No statistically significant differences between the treatment groups were shown for the outcomes "SAEs", "discontinuation due to AEs", "infections" and "serious infections". In each case, this resulted in no hint of greater or lesser harm from upadacitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven for each of these outcomes.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, probability and extent of the added benefit of the drug upadacitinib in comparison with the ACT for adult patients for whom a first therapy with bDMARDs or tsDMARDs is indicated are assessed as follows:

In the overall consideration, there were exclusively positive effects of upadacitinib + MTX in comparison with adalimumab + MTX for adult patients for whom a first therapy with bDMARDs or tsDMARDs is indicated. This concerns outcomes of all outcome categories except side effects. Indications of an added benefit were shown for clinical remission and low disease activity, the key outcomes in the therapeutic indication. In addition, there were several hints of an added benefit, e.g. also for health-related quality of life.

In summary, there is an indication of considerable added benefit of upadacitinib + MTX versus adalimumab + MTX for adult patients with moderate to severe active rheumatoid arthritis for whom a first therapy with bDMARDs or tsDMARDs is indicated.

No data are available for the patient group for whom monotherapy with upadacitinib is an option. The added benefit is not proven for this patient group.

Research question 3: adult patients with inadequate response or intolerance to pretreatment with one or more bDMARDs and/or tsDMARDs

Study pool and study characteristics

The study pool of the benefit assessment of upadacitinib in comparison with the ACT for research question 3 consisted of the RCT SELECT-CHOICE, which compared upadacitinib + csDMARDs with abatacept + csDMARDs. The SELECT-CHOICE study is exclusively suitable to derive conclusions on the added benefit of upadacitinib for the combination therapy with MTX, based on a subpopulation.

The SELECT-CHOICE study is randomized, double-blind study on the comparison of upadacitinib with abatacept, each in combination with csDMARD treatment. The study included adult patients with moderate to severe active rheumatoid arthritis who had responded inadequately to, or had not tolerated, pretreatment of at least 3 months with ≥ 1 bDMARD (except abatacept). In addition, the patients had been receiving csDMARD(s) on a stable dose

[3] 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, added benefit not proven, or less benefit). For further details see [1,2].

within the last 4 weeks before the first dose of the study medication and had to continue this therapy as concomitant treatment during the study.

A total of 657 patients were randomly allocated in a 1:1 ratio to upadacitinib + csDMARD(s) and abatacept + csDMARD(s).

The patients randomized as of protocol amendment 4 were included for the present benefit assessment. Treatment with upadacitinib in these patients was in compliance with the SPC. Treatment with abatacept was also in compliance with the corresponding SPC.

During the study, from week 12, predefined therapy adjustments were made according to local requirements if certain criteria for response to treatment were not met. Treatment switch to the respective other study arm was not possible in the study.

The double-blind, randomized treatment phase of the SELECT-CHOICE study was 24 weeks. Analyses at the end of the randomized treatment phase of 24 weeks were used for the study.

Primary outcome of the study was the change in DAS28 (C-reactive protein [CRP]) at week 12. Patient-relevant outcomes on morbidity, health-related quality of life and AEs were additionally recorded.

Relevant subpopulation for research question 3

In accordance with the approval, only the subpopulation who received treatment with upadacitinib or abatacept, each in combination with MTX, was relevant for the present benefit assessment. These were 223 patients in the intervention arm and 215 patients in the comparator arm.

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes was rated as low for the SELECT-CHOICE study.

The risk of bias for the results for the outcome “all-cause mortality” and for all side effect outcomes was rated as high.

The risk of bias for the results of the outcomes “clinical remission” and “low disease activity”, recorded with SDAI ≤ 3.3 and CDAI ≤ 2.8 or CDAI ≤ 10 and SDAI ≤ 11, was rated as high. In case of statistically significant results, however, in addition to the primary analysis in which patients with missing values were included as non-responders, sensitivity analyses were used in which missing values were imputed using alternative strategies. If the results were consistent, the certainty of conclusions of the results was not downgraded despite the high risk of bias.

The risk of bias for the results of the outcome “clinical remission”, recorded with the Boolean definition, and the risk of bias for the results of further outcomes of the categories of morbidity and health-related quality of life was rated as low.

Results

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 upadacitinib + MTX in comparison with abatacept + MTX; an added benefit is therefore not proven.

Morbidity

Clinical remission

The outcome "clinical remission" was operationalized using the CDAI ≤ 2.8, the SDAI ≤ 3.3, or the Boolean definition according to ACR/EULAR. The assessment of clinical remission was primarily based on the CDAI ≤ 2.8.

For the outcome "clinical remission", no statistically significant difference between the treatment groups was shown on the basis of the CDAI ≤ 2.8. This was also shown in the Boolean definition. A statistically significant difference in favour of upadacitinib + MTX was shown for clinical remission operationalized using the SDAI ≤ 3.3.

However, there was an effect modification by the characteristic "age" for the primarily used CDAI ≤ 2.8. A statistically significant difference in favour of upadacitinib + MTX was shown for patients aged ≥ 65 years. The sensitivity analyses using alternative imputation strategies confirmed this effect regarding statistical significance. This resulted in an indication of an added benefit of upadacitinib + MTX versus abatacept + MTX for patients aged ≥ 65 years. For patients aged < 40 years and patients aged ≥ 40 years to < 65 years, however, there was no hint of an added benefit of upadacitinib + MTX versus abatacept + MTX; an added benefit is therefore not proven.

Low disease activity

The outcome "low disease activity" was operationalized as reaching the criteria of CDAI ≤ 10 and SDAI ≤ 11. The assessment of low disease activity was primarily based on the CDAI ≤ 10.

No statistically significant difference between the treatment groups was shown for the outcome "low disease activity" on the basis of the CDAI ≤ 10. On the basis of the SDAI ≤ 11, there was a statistically significant difference in favour of upadacitinib + MTX.

For the CDAI ≤ 10, however, there was an effect modification by the characteristic "disease activity at baseline", defined with the threshold value of the DAS28 (CRP) for high disease activity. A statistically significant difference in favour of upadacitinib + MTX was shown for patients with high disease activity at baseline. The sensitivity analyses using alternative imputation strategies confirmed this effect regarding statistical significance. This resulted in an indication of an added benefit of upadacitinib + MTX versus abatacept + MTX for patients with high disease activity at baseline (DAS28 [CRP] > 5.1). For patients without high disease

activity at baseline (DAS28 [CRP] ≤ 5.1), however, there was no hint of an added benefit of upadacitinib + MTX versus abatacept + MTX; an added benefit is therefore not proven.

Tender joints, swollen joints, pain (VAS)

For each of the outcomes "tender joints", „swollen joints" and "pain" (VAS), no statistically significant difference between the treatment groups was shown based on the mean differences. In each case, this resulted in no hint of an added benefit of upadacitinib + MTX in comparison with abatacept + MTX; an added benefit is therefore not proven for each of these outcomes.

Patient assessment of disease activity (VAS), physical functioning (HAQ-DI), fatigue (FACIT-Fatigue)

There was no statistically significant difference between the treatment groups for each of the outcomes "patient assessment of disease activity (VAS)", "physical functioning (HAQ-DI)" and "fatigue (FACIT-Fatigue)". In each case, this resulted in no hint of an added benefit of upadacitinib + MTX in comparison with abatacept + MTX; an added benefit is therefore not proven for each of these outcomes.

Morning stiffness (severity [NRS], duration)

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome "severity (NRS) of morning stiffness". The SMD in the form of Hedges' g was considered to check the relevance of the result. However, the 95% CI was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect was relevant. There was no statistically significant difference between the treatment groups for the duration of morning stiffness. This did not result in a hint of an added benefit of upadacitinib + MTX in comparison with abatacept + MTX for the severity (NRS) or for the duration of morning stiffness; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome "health status (EQ-5D VAS)". The SMD in the form of Hedges' g was considered to check the relevance of the result. However, the 95% CI was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect was relevant. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with abatacept + MTX; an added benefit is therefore not proven.

Health-related quality of life

SF-36v2 – Physical and Mental Component Summary

No statistically significant difference between the treatment groups was shown for the Physical Component Summary or for the Mental Component Summary of the SF-36v2. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with abatacept + MTX for the outcome "health-related quality of life (SF-36v2)"; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs, infections, serious infections

No statistically significant differences between the treatment groups were shown for the outcomes "SAEs", "discontinuation due to AEs", "infections" and "serious infections". In each case, this resulted in no hint of greater or lesser harm from upadacitinib + MTX in comparison with abatacept + MTX; greater or lesser harm is therefore not proven for each of these outcomes.

Probability and extent of added benefit, patient groups with therapeutically important added benefit

On the basis of the results presented, probability and extent of the added benefit of the drug upadacitinib in comparison with the ACT for adult patients with inadequate response or intolerance to pretreatment with one or more bDMARDs and/or tsDMARDs are assessed as follows:

In the overall consideration, there were exclusively positive effects of upadacitinib + MTX in comparison with abatacept + MTX for adult patients with inadequate response or intolerance to pretreatment with one or more bDMARDs and/or tsDMARDs. This concerns the outcomes "clinical remission" and "low disease activity", in each case for different subgroups. For both outcomes, the sensitivity analyses confirmed the primary analyses in the relevant subgroups, both regarding statistical significance and extent. The advantage of upadacitinib + MTX, resulting for the primary treatment goal of clinical remission, concerned the notably smaller subgroup of patients aged ≥ 65 years. The larger subgroup of patients with high disease activity at baseline, for whom there was an advantage of upadacitinib + MTX for the alternative treatment goal of low disease activity, in contrast, constituted the majority of the study population. In addition, it can be assumed on the basis of the information on the total population of the SELECT-CHOICE study that this subgroup also included patients of the age group of ≥ 65 years. However, information on the extent to which the two subgroups overlap is not available for the relevant subpopulation of the study. Thus, the subgroup of patients with high disease activity at baseline was used for the derivation of the added benefit.

In summary, there is an indication of a minor added benefit of upadacitinib + MTX versus abatacept + MTX for adult patients with moderate to severe active rheumatoid arthritis with high disease activity (DAS28 [CRP] > 5.1) and inadequate response or intolerance to pretreatment with one or more bDMARDs and/or tsDMARDs.

No data are available for patients for whom monotherapy with upadacitinib is an option. The added benefit is not proven for this patient group.

Probability and extent of added benefit – Summary

The result of the assessment of the added benefit of upadacitinib in comparison with the ACT is summarized in Table 3.

Table 3: Upadacitinib – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
Adults with moderate to severe active rheumatoid arthritis			
1	Patients without poor prognostic factors[b] who have responded inadequately to, or who are intolerant to prior treatment with one csDMARD[c] (including MTX)	Alternative csDMARDs[c] if suitable (e.g. MTX, leflunomide) as monotherapy or combination therapy	Added benefit not proven
2	Patients for whom a first therapy with bDMARDs or tsDMARDs is indicated[d]	bDMARDs or tsDMARDs (abatacept or **adalimumab** or baricitinib or certolizumab pegol or etanercept or golimumab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability)	Combination with MTX: indication of considerable added benefit Monotherapy: added benefit not proven
3	Patients who have responded inadequately to, or who are intolerant to prior treatment with one or more bDMARDs and/or tsDMARDs	Switching of bDMARD or tsDMARD therapy (**abatacept** or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability; or, in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on prior therapy[e]	Combination with MTX: ▪ Patients with high disease activity (DAS28 [CRP] > 5.1): ▫ indication of minor added benefit ▪ Patients without high disease activity (DAS28 [CRP] ≤ 5.1): ▫ added benefit not proven Monotherapy: added benefit not proven

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. Poor prognostic factors: detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antigen 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. In the G-BA's specification of the ACT, csDMARDs are referred to as "classical DMARDs". The present benefit assessment uses the term "csDMARDs".
d. This comprises both patients with poor prognostic factors who have responded inadequately to, or who have not tolerated previous treatment with one csDMARD (including MTX), and patients who have responded inadequately to or have not tolerated previous treatment with several csDMARDs (including MTX).
e. Switching the mode of action should be considered depending on the prior therapy.

ACT: appropriate comparator therapy; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate; tsDMARD: targeted synthetic DMARD

The approach for deriving an overall conclusion on the 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 is the assessment of the added benefit of upadacitinib as monotherapy or in combination with MTX in comparison with the ACT in adult patients with moderate to severe active rheumatoid arthritis who have responded inadequately to, or who are intolerant to one or more DMARDs.

The G-BA differentiated between 3 patient groups in its specification of the ACT in the approved therapeutic indication. This resulted in 3 research questions for the assessment; their therapeutic indications and ACTs are presented in Table 4.

Table 4: Research questions of the benefit assessment of upadacitinib

Research question	Subindication	ACT[a]
Adults with moderate to severe active rheumatoid arthritis		
1	Patients without poor prognostic factors[b] who have responded inadequately to, or who are intolerant to prior treatment with one csDMARD[c] (including MTX)	Alternative csDMARDs[c] if suitable (e.g. MTX, leflunomide) as monotherapy or combination therapy
2	Patients for whom a first therapy with bDMARDs or tsDMARDs is indicated[d]	bDMARDs or tsDMARDs (abatacept or **adalimumab** or baricitinib or certolizumab pegol or etanercept or golimumab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability)
3	Patients who have responded inadequately to, or who are intolerant to prior treatment with one or more bDMARDs and/or tsDMARDs	Switching of bDMARD or tsDMARD therapy (**abatacept** or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability; or, in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on prior therapy[e]

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. Poor prognostic factors: detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antigen 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. In the G-BA's specification of the ACT, csDMARDs are referred to as "classical DMARDs". The present benefit assessment uses the term "csDMARDs".
d. This comprises both patients with poor prognostic factors who have responded inadequately to, or who have not tolerated previous treatment with one csDMARD (including MTX), and patients who have responded inadequately to or have not tolerated previous treatment with several csDMARDs (including MTX).
e. Switching the mode of action should be considered depending on the prior therapy.

ACT: appropriate comparator therapy; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate; tsDMARD: targeted synthetic DMARD

For easier presentation and better readability, the present benefit assessment uses the following terms for the research questions in the running text:

- Research question 1: adult patients without poor prognostic factors and with inadequate response or intolerance to pretreatment with one csDMARD
- Research question 2: adult patients for whom a first therapy with bDMARDs or tsDMARDs is indicated
- Research question 3: adult patients with inadequate response or intolerance to pretreatment with one or more bDMARDs and/or tsDMARDs

Research questions 1, 2 and 3 of the present benefit assessment correspond to the patient groups a, b and c in the G-BA's specification of the ACT.

The company followed the G-BA's specification of the ACT. From the treatment options presented, the company chose adalimumab for research question 2 and abatacept for research question 3.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data presented 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 Research question 1: adult patients without poor prognostic factors and with inadequate response or intolerance to pretreatment with one csDMARD

2.3.1 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 upadacitinib (status: 2 December 2019)
- bibliographical literature search on upadacitinib (last search on 5 November 2019)
- search in trial registries for studies on upadacitinib (last search on 5 November 2019)

To check the completeness of the study pool:

- search in trial registries for studies on upadacitinib (last search on 22 January 2020)

In its dossier, the company presented no study on research question 1. No relevant study was identified from the check either.

2.3.2 Results on added benefit

The company presented no data for the assessment of the added benefit of upadacitinib in comparison with the ACT for adult patients who have no poor prognostic factors and have responded inadequately to or have not tolerated previous treatment with one csDMARD. This resulted in no hint of an added benefit of upadacitinib in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

The company presented no data for the assessment of the added benefit of upadacitinib in adult patients who have no poor prognostic factors and have responded inadequately to or have not tolerated previous treatment with one csDMARD. An added benefit of upadacitinib 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 this patient group.

2.4 Research question 2: adult patients for whom a first therapy with bDMARDs or tsDMARDs is indicated

2.4.1 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 upadacitinib (status: 2 December 2019)
- bibliographical literature search on upadacitinib (last search on 5 November 2019)
- search in trial registries for studies on upadacitinib (last search on 5 November 2019)

To check the completeness of the study pool:

- search in trial registries for studies on upadacitinib (last search on 22 January 2020)

No additional relevant study was identified from the check.

2.4.1.1 Studies included

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

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

Study	Study category			Available sources		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and sources on the G-BA website (yes/no [citation])
M14-465 (SELECT COMPARE[c])	Yes	Yes	No	Yes [3-5]	Yes [6-8]	Yes [9,10]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this designation.

G-BA: Federal Joint Committee; MTX: methotrexate; RCT: randomized controlled trial; vs.: versus

The study pool of the benefit assessment of upadacitinib in comparison with the ACT for research question 2 consisted of the RCT SELECT-COMPARE and corresponded to the study pool of the company. The study compared upadacitinib + MTX with adalimumab + MTX. The SELECT-COMPARE study is exclusively suitable to derive conclusions on the added benefit of upadacitinib for the combination therapy with MTX.

2.4.1.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: upadacitinib + MTX vs. adalimumab + MTX

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
SELECT-COMPARE	RCT, double-blind, parallel	Patients ≥ 18 years with moderate to severe active rheumatoid arthritis ▪ with inadequate response under MTX ▪ with continuous treatment with MTX for ≥ 3 months and on a stable dose ≥ 4 weeks before the first dose of the study medication (15–25 mg per week)	Upadacitinib + MTX (N = 651) placebo + MTX (N = 651)[b] adalimumab + MTX (N = 327)	Screening: 35 days Period 1: ▪ double-blind treatment for 48 weeks Period 2: ▪ open-label extension phase for up to 5 years[c] Follow-up observation[d]: ▪ until 70 days after the last dose of the study medication	286 centres in 41 countries[e] 12/2015–ongoing Data cut-off at week 26: 2 Feb 2018[f] Data cut-off at week 48: 6 Jul 2018[g] Data cut-off at week 72: 26 Dec 2018[h]	Primary: ▪ ACR20 at week 12 (USA/FDA) ▪ DAS28 < 2.6 at week 12 (EU/EMA)[i] Secondary: ▪ morbidity ▪ health-related quality of life ▪ AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. As of week 26, all patients in the placebo arm were switched to upadacitinib. The arm is not relevant for the assessment and is no longer shown in the following tables.
c. The study medication received by the patients at the end of period 1 was continued in period 2. Patients with < 20% improvement in swollen and tender joint count compared with baseline on 2 consecutive visits from week 48 had to end the study medication.
d. Outcome-specific information is provided in Table 8.
e. Argentina, Australia, Belarus, Belgium, Bosnia-Herzegovina, Brazil, Bulgaria, Canada, Chile, Colombia, Croatia, Czech Republic, Estonia, France, Germany, Greece, Hong Kong, Hungary, Israel, Italy, Kazakhstan, Latvia, Lithuania, Malaysia, Mexico, New Zealand, Poland, Portugal, Puerto Rico, Romania, Russia, Serbia, Slovakia, South Africa, South Korea, Spain, Taiwan, Turkey, Ukraine, United Kingdom, USA.
f. After all randomized patients have reached week 26.
g. After all randomized patients have completed the double-blind treatment phase (week 48).
h. After all randomized patients have reached week 72.
i. Prior to protocol amendment 2 (8 January 2016), the primary outcome was the change in mTSS at week 26.

ACR20: 20% improvement in American College of Rheumatology criteria; AE: adverse event; CRP: C-reactive protein; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; EMA: European Medicines Agency; FDA: US Food and Drug Administration; mTSS: modified Total Sharp Score; MTX: methotrexate; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: upadacitinib + MTX vs. adalimumab + MTX

Study	Intervention	Comparison
SELECT-COMPARE	Upadacitinib 15 mg orally, once/day[a] + placebo subcutaneously, every 2 weeks	Adalimumab 40 mg subcutaneously, every 2 weeks[a] + placebo orally, once/day
	Allowed prior and concomitant treatment ▪ MTX: continuation of the oral or parenteral MTX therapy maintained for ≥ 3 months, ≥ 4 weeks on a stable dose (15 mg to 25 mg per week) before the first dose of the study medication; in case of intolerance of dosages ≥ 12.5 mg/week: stable dose of ≥ 10 mg/week ▪ Folic acid/folinic acid supplementation ▪ NSAIDs, paracetamol on a stable dose ≥ 1 week before the first dose of the study medication until week 26[b] ▪ oral corticosteroids (≤ 10 mg prednisone or equivalent daily) or inhaled corticosteroids on a stable dose ≥ 4 weeks before first dose of the study medication until week 26[b, c] ▪ corticosteroids (IA, IM, IV, etc.): ≤ 2 injections from week 26[d] ▪ further csDMARDs (excl. MTX): no earlier than week 26[e] simultaneous administration of ≤ 2 csDMARDs (except combination of MTX and leflunomide)[f] **Non-permitted pretreatment** ▪ JAK inhibitors ▪ bDMARD ≥ 3 months with inadequate response[g] **Non-permitted concomitant treatment** ▪ bDMARDs[f] ▪ strong opiates (e.g. oxycodone, morphine) ▪ strong CYP3A inhibitors and inducers ▪ traditional Chinese medicine ▪ live vaccines	

a. Patients with inadequate response received the following treatment adjustments:
- Patients with < 20% improvement in swollen and tender joint count at weeks 14, 18 or 22 in comparison with baseline switched to the respective other treatment arm, while maintaining blinding.
- Patients who had not achieved low disease activity (defined as CDAI ≤ 10) at week 26 switched to the respective other treatment arm, while maintaining blinding.
- From week 48, patients with < 20% improvement in swollen and tender joint count in comparison with baseline on 2 consecutive visits had to end the study medication.

b. From week 26, adjustments according to local requirements were allowed.
c. From week 26, high-dose corticosteroid treatments (prednisone equivalent ≤ 0.5 mg/kg body weight/day) in case of flare-ups were allowed for a maximum of 3 days.
d. Not permitted within 8 weeks before the first dose of the study medication until week 26; not allowed within 21 days before a study visit; injected joints were rated as "not assessable" for the following 3 months.
e. Regarding csDMARDs, the study documents contain contradictory information on the time point from which adjustments according to local requirements were allowed (week 48 or week 26).
f. csDMARDs (except MTX) and bDMARDs had to be discontinued at least 4 weeks before the first dose of the study medication.
g. According to the study protocol allowed in a maximum of 20% of the study population: pretreatment with bDMARD: ≤ 1 bDMARD (except adalimumab) with treatment duration < 3 months or discontinuation of treatment due to intolerance (irrespective of the treatment duration).

bDMARD: biologic DMARD; CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic DMARD; CYP3A: cytochrome P450 3A; DMARD: disease-modifying antirheumatic drug; IA: intraarticular; IM: intramuscular; IV: intravenous; JAK: Janus kinase; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; vs.: versus

The SELECT-COMPARE study is a 3-arm, randomized, double-blind study on the comparison of upadacitinib with adalimumab and placebo, each in combination with MTX.

The study included adult patients with moderate to severe active rheumatoid arthritis who have an inadequate response to MTX.

Diagnosis of rheumatoid arthritis had to be conducted at least 3 months earlier and according to the 2010 ACR/EULAR classification criteria [11]. In addition, patients had to fulfil the following criteria to be eligible for enrolment:

- ≥ 6 swollen and ≥ 6 tender joints, based on 66 or 68 joint counts respectively
- CRP ≥ 5 mg/L
- either ≥ 3 bone erosions or ≥ 1 bone erosion and a positive rheumatoid factor or a positive cyclic citrullinated peptide (CCP) antibody.

The patients had to have received continuous treatment with MTX for ≥ 3 months, which had to be on a stable dose within the last 4 weeks before the first dose of the study medication. This dosage was continued as concomitant treatment during the study. Concomitant treatment with other csDMARDs – except MTX – was not allowed within the study until week 26.

A total of 1629 patients were randomly allocated in a ratio of 2:1:2 to the 3 treatment arms of upadacitinib + MTX (N = 651), adalimumab + MTX (N = 327) and placebo + MTX (N = 651). Besides pretreatment with bDMARD (yes/no), stratification was by geographical region. For the present benefit assessment, only the study arms of upadacitinib + MTX and adalimumab + MTX are relevant; therefore, the subsequent description only refers to these 2 study arms.

Treatment with upadacitinib and adalimumab was in compliance with the recommendations of the respective SPCs [12,13]. The planned double-blind, randomized treatment phase was 48 weeks. Treatment of the patients is continued as open-label treatment in the subsequent, still ongoing extension phase.

For the EMA, the primary outcome of the study was defined as the proportion of patients with DAS28 < 2.6; for the FDA, it was defined as the proportion of patients with ACR20, each at week 12. Patient-relevant outcomes on morbidity, health-related quality of life and AEs were additionally recorded.

Table 8 shows the planned duration of follow-up observation of the patients for the different outcome categories in the double-blind treatment phase until week 48. The planned duration of the follow-up observation in the extension phase is not presented, as this phase is not relevant in the present situation (see below).

Table 8: Planned duration of follow-up observation (double-blind treatment phase [48 weeks]) – RCT, direct comparison: upadacitinib + MTX vs. adalimumab + MTX

Study **Outcome category** **Outcome**	**Planned follow-up observation**
SELECT-COMPARE	
Mortality	
All-cause mortality	▪ See information on the outcome category of side effects
Morbidity	
All outcomes in the category of morbidity	▪ In case of premature study discontinuation: study visit within 2 weeks ▪ After end of therapy: no follow-up planned
▪ Health-related quality of life	
SF-36v2	▪ In case of premature study discontinuation: study visit within 2 weeks ▪ After end of therapy: no follow-up planned
Side effects	
All outcomes in the category of side effects	▪ After completion of 48 weeks under study medication and subsequent participation in the open-label extension phase: no follow-up planned ▪ After completion of 48 weeks under study medication without subsequent participation in the open-label extension phase: ▫ 30 days after the last administration of the study medication ▫ 70-day follow-up: after the last dose for patients with subcutaneous study medication[a, b] ▪ In case of premature treatment discontinuation with continued study participation: study visit within 2 weeks, then: ▫ 30-day follow-up[c] ▫ 70-day follow-up: after the last dose for patients with subcutaneous study medication[a, b, c] ▪ In case of premature study discontinuation: study visit within 2 weeks, then: ▫ optional 30-day follow-up ▫ optional 70-day follow-up: after the last dose for patients with subcutaneous study medication[a, b]

a. Not applicable to patients who have meanwhile started commercial adalimumab therapy.
b. It is not clear from the available data whether or not the duration of follow-up observation was different for the 2 treatment arms, as there was discrepant information.
c. Not applicable to patients with regular study visit in the double-blind treatment phase at this time point.

MTX: methotrexate; RCT: randomized controlled trial; SF-36v2: Short Form (36) – version 2 Health Survey; vs.: versus

No follow-up observation after the end of therapy was planned for outcomes on morbidity and health-related quality of life. In case of premature study discontinuation, a follow-up visit took place within 2 weeks after the last dose of the study medication. It can be assumed that the duration of follow-up observation for the outcomes of the categories of mortality and side effects for patients with premature treatment discontinuation and for patients who ended the study after completion of the double-blind phase of 48 weeks differed under certain conditions for the 2 study arms: 30 days in the intervention arm and 70 days in the comparator arm. This

was not clear from the study documents. However, a large proportion of the patients (about 87%) continued the study in the open-label extension phase after completion of the double-blind phase. In this case, no follow-up observation of AEs was planned. Further information on the duration of the follow-up observation is not available. It therefore remains unclear for how many patients follow-up observation was actually different at week 26, which was the relevant date of analysis, and the other time points (see below). This was considered in the assessment of the risk of bias (see Section 2.4.2.2).

In the SELECT-COMPARE study, therapy adjustments were made at predefined time points if certain criteria for response to treatment were not met. At weeks 14, 18 or 22, patients with < 20% improvement in swollen and tender joint count in comparison with baseline switched to the respective other treatment arm in the framework of a rescue therapy, while maintaining blinding. At week 26, such a switch was conducted for patients who had not achieved low disease activity, defined as CDAI ≤ 10. In addition, as of week 26, both adjustments of the concomitant medication, e.g. with corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs), according to local guidelines, and concomitant treatment with further csDMARDs in addition to MTX were permitted, whereby no more than 2 csDMARDs could be given simultaneously. A combination of MTX and leflunomide was the exception, however. Concomitant treatment with further csDMARDs in addition to MTX does not comply with the recommendations of the SPCs of upadacitinib [13] or adalimumab [12]. It is unclear how many patients received such treatment as therapy adjustment. This had no consequence for the present benefit assessment, however, as the analyses at week 26 were used for the assessment of the added benefit (for reasons, see the following explanations and Section 2.7.4.1 of the full dossier assessment). From week 48, patients with < 20% improvement in swollen and tender joint count in comparison with baseline on 2 consecutive visits had to end the study medication.

Dates of analysis

Analyses for 3 time points are available for the ongoing SELECT-COMPARE study:

- analyses at week 26, based on the predefined data cut-off from 2 February 2018, after all randomized patients had reached week 26
- analyses at week 48, based on the data cut-off from 6 July 2018, after all randomized patients had completed the double-blind treatment phase (week 48)
- analyses at week 72, based on the data cut-off from 26 December 2018, after all randomized patients had reached week 72; thus the analyses also include data after unblinding of treatment; according to the company, analyses relevant for the regulatory authorities.

For outcomes on morbidity and health-related quality of life, the company used analyses at week 26, arguing that the number of patients with treatment switch was moderate at this time point, so that potential biases in this regard could be addressed with adequate methods of analysis. In addition, the company presented supplementary analyses at the time points of

week 12 and week 48 for all benefit outcomes. The company used analyses at week 48 for the outcomes on mortality and side effects, arguing that the event time analyses presented by the company were an adequate analysis.

Contrary to the company's approach, the present benefit assessment used analyses at week 26 for all outcomes included. This is justified below, using the information provided in Table 9.

Table 9 shows how many patients had switched to the other treatment arm as rescue therapy by week 48, how many patients had discontinued the therapy or study by week 72, and how many patients had received the originally allocated therapy by week 72.

Table 9: Number of patients under allocated treatment, with treatment switch, treatment discontinuation, and study discontinuation – RCT, direct comparison: upadacitinib + MTX vs. adalimumab + MTX

Study Characteristics Time point	Upadacitinib + MTX N[a] = 651	Adalimumab + MTX N[a] = 327
SELECT-COMPARE		
Under rescue therapy, n (%)		
Week 14	78 (12.0)	56 (17.1)
Week 18	107 (16.4)[b]	70 (21.4)[b]
Week 22	125 (19.2)[b]	77 (23.5)[b]
Week 26	126 (19.4)	82 (25.1)
Week 48	252 (38.7[b])	159 (48.6[b])
Treatment discontinuation, n (%)		
Week 26	51 (7.8)[b, c]	39 (11.9)[b, c]
Week 48	75 (11.5)[d]	58 (17.7)[d]
Week 72[e]	130 (20.0)[b, f]	74 (22.6)[b, f]
On originally allocated therapy, n (%)		
Week 26	481 (73.9)[b]	208 (63.6)[b]
Week 48	343 (52.5[b])	127 (38.8[b])
Week 72[e]	324 (49.8[b])	122 (37.3[b])
Study discontinuation, n (%)		
Week 26	61 (9.4)[b]	41 (12.5)[b]
Week 48	71 (10.9)[g]	49 (15.0)[g]
Week 72[e]	111 (17.1)[b, h]	59 (18.0)[b, h]

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. Thereof patients with discontinuation of rescue therapy: in the upadacitinib arm: N = 7, in the adalimumab arm: N = 2.
d. Thereof patients with discontinuation of rescue therapy: in the upadacitinib arm: N = 19, in the adalimumab arm: N = 17.
e. Upadacitinib: 576 (88.5%), adalimumab: 277 (84.7%) of the patients were included in period 2 (week 48 to week 72).
f. Thereof patients with discontinuation of rescue therapy: in the upadacitinib arm: N = 56, in the adalimumab arm: N = 28.
g. Thereof patients with discontinuation under rescue therapy: in the upadacitinib arm: N = 18, in the adalimumab arm: N = 14.
h. Thereof patients with discontinuation under rescue therapy: in the upadacitinib arm: N = 45, in the adalimumab arm: N = 21.

MTX: methotrexate; n: number of patients in the category; N: number of randomized patients;
RCT: randomized controlled trial; vs.: versus

Until week 26, 1 quarter of the patients had already switched from the comparator therapy of adalimumab + MTX to upadacitinib + MTX as rescue therapy. At week 48, this applied to almost half of the patients in the comparator arm. The difference in patients with rescue therapy

between the treatment arms increased from about 6 percentage points at week 26 to about 10 percentage points at week 48. The joint consideration of patients with treatment switch and discontinuation shows that, in the study, only about 39% of the patients who had been randomized to the comparator therapy were being treated with adalimumab + MTX at week 48.

Treatment regimens with strict therapy adjustments in case of inadequate response after 3 to 6 months of treatment are recommended according to current German and European guidelines for the treatment of rheumatoid arthritis [14,15]. Study designs that provide for therapy adjustment to a standard therapy approved in the therapeutic indication are therefore generally desirable. The switch in the SELECT-COMPARE study from adalimumab to upadacitinib, which was not yet to be considered a standard therapy at the time of approval, may be a potentially biasing factor for the results of the benefit assessment, however. In the present situation, the risk of bias was more pronounced at week 48 than at week 26 due to the notably higher proportion of patients with such a switch. In addition, the proportion of patients who, contrary to the approval of upadacitinib and adalimumab, received treatment adjustments by addition of further csDMARDs from week 26 is unclear. Therefore, analyses at week 26 were used for the present benefit present assessment (see also Section 2.7.4.1 of the full dossier assessment).

Types of analysis

In the SELECT-COMPARE study, it was planned as primary analysis for binary variables to impute all patients with values after switch of therapy and patients with missing values at the date of analysis by means of non-responder imputation (NRI). The company referred to these analyses as “RNRI” (NRI after switch to rescue therapy). As a sensitivity analysis in the SELECT-COMPARE study, analyses for binary variables were planned that take into account actually observed values, without imputation of missing values and without imputation of values after a switch of therapy. The company used analyses with RNRI imputation as primary analysis for binary outcomes of the categories of morbidity and health-related quality of life. In addition, the company presented sensitivity analyses in which only missing values were imputed as non-response, whereas values of patients after switch of therapy were not imputed. The company referred to these analyses as “NRI imputation”. For outcomes with high risk of bias, the company considered these sensitivity analyses with NRI imputation to check whether the certainty of conclusions of the results of the RNRI analyses had to be downgraded due to the high risk of bias. In addition, the company presented supplementary event time analyses for binary outcomes at the time point of week 26.

For continuous variables, it was planned in the SELECT-COMPARE study to impute values after switch of therapy with the last observed values before the switch of therapy (last observation carried forward [LOCF]). Sensitivity analyses for continuous variables were not planned in the SELECT-COMPARE study. The company presented analyses in which both values after a switch of therapy and missing values were imputed with the last value before the switch of therapy or with the last observed value, and referred to these analyses as “rescue last observation carried forward (RLOCF)”. It used these analyses as primary analysis for

continuous outcomes of the category of morbidity. In addition, the company presented sensitivity analyses in which values after switch of therapy were not imputed, but only missing values, and referred to these analyses as “last observation carried forward (LOCF)”. For outcomes with high risk of bias, the company considered these sensitivity analyses with LOCF imputation to check whether the certainty of conclusions of the results of the RLOCF analyses had to be downgraded due to the high risk of bias.

For AEs, analyses on the basis of naive rates in which patients were censored after switch of therapy were planned as primary analysis in the SELECT-COMPARE study. The company did not use these analyses, but presented event time analyses at week 48 in which patients were censored after switch of therapy for outcomes of the categories of mortality and side effects.

Concurring with the company, the primary analysis for outcomes of the categories of morbidity and health-related quality of life for the present benefit assessment used analyses with RNRI imputation for binary outcomes, and analyses with RLOCF imputation for continuous outcomes. For outcomes with high risk of bias, the sensitivity analyses with or NRI or LOCF imputation presented by the company were additionally used to check whether the certainty of conclusions of the results had to be downgraded due to the high risk of bias. Sensitivity analyses were only considered for outcomes for which there were statistically significant and clinically relevant results besides a high risk of bias. See Sections 2.4.2.3 and 2.4.3.2 for information on the concrete approach used in these outcomes.

For outcomes of the categories of mortality and side effects, the Institute conducted its own calculations with the effect measure relative risk (RR) on the basis of the naive rates in which patients were censored after switch of therapy. Sensitivity analyses were not available for these outcomes. As described above, analyses at week 26 were used for all outcomes (see also Sections 2.7.4.1 and 2.7.4.2 of the full dossier assessment).

Patient characteristics

Table 10 shows the characteristics of the patients in the study included.

Table 10: Characteristics of the study population – RCT, direct comparison: upadacitinib + MTX vs. adalimumab + MTX (multipage table)

Study Characteristics Category	**Upadacitinib + MTX N[a] = 651**	**Adalimumab + MTX N[a] = 327**
SELECT-COMPARE		
Age [years], mean (SD)	54 (12)	54 (12)
Sex [F/M], %	80/20	79/21
Region, n (%)		
North America	122 (19)	60 (18)
South/Middle America	173 (27)	86 (26)
Eastern Europe	262 (40)	132 (40)
Western Europe	35 (5)	19 (6)
Asia	21 (3)	10 (3)
Other	38 (6)	20 (6)
Disease duration: time between first diagnosis and randomization [years], median [Q1; Q3]	5.5 [2.3; 11.5]	5.5 [2.3; 11.9]
Rheumatoid factor status, n (%)		
Positive	521 (80)	265 (81)
Negative	130 (20)	62 (19)
Anti-CCP, n (%)		
Positive	525 (81)	264 (81)
Negative	126 (19)	63 (19)
DAS28 (CRP), (disease activity at baseline), mean (SD)	5.8 (1.0)	5.9 (1.0)
DAS28 (CRP), (disease activity at baseline), n (%)		
≤ 5.1	149 (23)	71 (22)
> 5.1	498 (76)	254 (77)
Unknown	4 (1[b])	2 (1[b])
Bone joint erosion score[c], mean (SD)	16.5 (26.4)	15.4 (23.1)
Joint space narrowing score[d], mean (SD)	17.5 (25.1)	19.2 (25.8)
mTSS, mean (SD)	34.0 (50.1)	34.5 (47.1)
Tender joint count[e], mean (SD)	15.0 (6.9)	15.1 (7.0)
Swollen joint count[e], mean (SD)	11.4 (5.6)	11.7 (5.5)
Functional status [HAQ-DI], mean (SD)	1.6 (0.6)	1.6 (0.6)
Pretreatment		
Number of csDMARDs, n (%)		
1	438 (67)	189 (58)
2	129 (20)	94 (29)
3	68 (10)	34 (10)
≥ 4	16 (2)	10 (3)
bDMARDs, n (%)		
Yes	54 (8)	34 (10)
No	597 (92)	293 (90)

Table 10: Characteristics of the study population – RCT, direct comparison: upadacitinib + MTX vs. adalimumab + MTX (multipage table)

Study Characteristics Category	Upadacitinib + MTX Na = 651	Adalimumab + MTX Na = 327
a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant. b. Institute's calculation. c. Based on the severity grade of the erosion in 32 joints of the hands and 12 joints of the feet. d. Based on the severity grade of joint space narrowing in 30 joints of the hands and 12 joints of both feet. e. Based on 28 joints. bDMARD: biologic DMARD; CCP: cyclic citrullinated peptide; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; csDMARD: conventional synthetic DMARD; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; DMARD: disease-modifying antirheumatic drug; F: female; HAQ-DI: Health Assessment Questionnaire-Disability Index; M: male; mTSS: modified Total Sharp Score; MTX: methotrexate; n: number of patients in the respective category; N: number of patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus		

The demographic and clinical characteristics between the 2 arms of the SELECT-COMPARE study were sufficiently balanced. The mean age of the patients was about 54 years, and most of them were women (about 80%). About 3 quarters of the patients had high disease activity at baseline (defined as DAS28 [CRP] > 5.1). The mean swollen joint count was about 11 of 28 joints, and about 80% of the patients had further poor prognostic factors, such as a positive rheumatoid factor or anti-CCP antibody status. About 60 to 70% of the patients had been pretreated with one csDMARD, the other patients with ≥ 2 csDMARDs. 8% to 10% of the study population received restricted pretreatment with bDMARDs for < 3 months or with discontinuation due to intolerance despite response to therapy. Thus, the vast majority of the study population concurred with the population relevant for this research question, i.e. adult patients for whom a first therapy with bDMARDs or tsDMARDs is indicated.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: upadacitinib + MTX vs. adalimumab + MTX

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

The risk of bias across outcomes was rated as low for the SELECT-COMPARE study. This concurs with the company's assessment.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - clinical remission
  - low disease activity
  - tender joints
  - swollen joints
  - pain (recorded using a VAS)
  - patient assessment of disease activity (recorded using a VAS)
  - physical functioning (recorded using the HAQ-DI)
  - fatigue (recorded using the FACIT-Fatigue)
  - morning stiffness (severity [recorded using an NRS], duration)
  - health status (recorded using the EQ-5D VAS)
- Health-related quality of life
  - recorded using the Physical and Mental Component Summary of the SF-36v2
- Side effects
  - SAEs
  - discontinuation due to AEs
  - infections (System Organ Class [SOC] "infections and infestations", AEs)
  - serious infections (SOC "infections and infestations", SAEs)
  - 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) (see Section 2.7.4.3.2 of the full dossier assessment).

Table 12 shows for which outcomes data were available in the included SELECT-COMPARE study.

Table 12: Matrix of outcomes – RCT, direct comparison: upadacitinib + MTX vs. adalimumab + MTX

Study	Outcomes															
	All-cause mortality	**Clinical remission (CDAI ≤ 2.8; SDAI ≤ 3.3; Boolean definition)[a]**	**Low disease activity (CDAI ≤ 10; SDAI ≤ 11)[a, b]**	**Tender joints[c]**	**Swollen joints[c]**	**Pain (VAS)**	**Patient assessment of disease activity (VAS)**	**Physical functioning (HAQ-DI)**	**Fatigue (FACIT-Fatigue)**	**Morning stiffness (severity [NRS], duration)**	**Health status (EQ-5D VAS)**	**Health-related quality of life (SF-36v2)**	**SAEs**	**Discontinuation due to AEs**	**Infections[d]**	**Serious infections[d]**
SELECT-COMPARE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. The derivation of the added benefit is primarily based on the CDAI, see Section 2.7.4.3.2 of the full dossier assessment.
b. Supplementary presentation: DAS28 (CRP) ≤ 3.2 and DAS28 (ESR) ≤ 3.2, see Appendix B.1 of the full dossier assessment.
c. Based on 28 joints.
d. All AEs of the MedDRA SOC "infections and infestations" are used for the recording of infections, and all SAEs for the recording of serious infections.

AE: adverse event; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; EQ-5D: European Quality of Life-5 Dimensions; ESR: erythrocyte sedimentation rate; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; MedDRA: Medical Dictionary for Regulatory Activities; MTX: methotrexate; NRS: numeric rating scale; 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

2.4.2.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: upadacitinib + MTX vs. adalimumab + MTX

Study		Outcomes																		
			Clinical remission[a]			Low disease activity[a, b]														
	Study level	All-cause mortality	CDAI ≤ 2.8	SDAI ≤ 3.3	Boolean definition	CDAI ≤ 10	SDAI ≤ 11	Tender joints[c]	Swollen joints[c]	Pain (VAS)	Patient assessment of disease activity (VAS)	Physical functioning (HAQ-DI)	Fatigue (FACIT-Fatigue)	Morning stiffness (severity [NRS], duration)	Health status (EQ-5D VAS)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Infections[d]	Serious infections[d]
SELECT-COMPARE	L	H[e, f]	L	L	L	H[e]	H[e]	H[e]	H[e]	H[e]	H[e]	H[e]	H[e]	H[e]	H[e]	H[e]	H[e, f]	H[e, f]	H[e, f]	H[e, f]

a. The derivation of the added benefit is primarily based on the CDAI, see Section 2.7.4.3.2 of the full dossier assessment.
b. Supplementary presentation: DAS28 (CRP) ≤ 3.2 and DAS28 (ESR) ≤ 3.2, see Appendix B.1 of the full dossier assessment.
c. Based on 28 joints.
d. All AEs of the MedDRA SOC "infections and infestations" are used for the recording of infections, and all SAEs for the recording of serious infections.
e. At week 26, the relevant time point of analysis, large proportions of patients with treatment switch (upadacitinib: 19.4%; adalimumab: 25.1%) and treatment discontinuation (upadacitinib: 7.8%; adalimumab: 11.9%).
f. Potential differences in follow-up observation periods between the treatment arms (upadacitinib: 30 days; adalimumab: 70 days).

AE: adverse event; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; EQ-5D: European Quality of Life-5 Dimensions; ESR: erythrocyte sedimentation rate; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; H: high; HAQ-DI: Health Assessment Questionnaire-Disability Index; L: low; MedDRA: Medical Dictionary for Regulatory Activities; MTX: methotrexate; NRS: numeric rating scale; 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 risk of bias was rated as high for the results on all outcomes, except for the outcome "clinical remission", as there was a large proportion of patients with treatment switch or discontinuation. There was an additional uncertainty for mortality and side effect outcomes resulting from the potential differences in follow-up observation periods between the study arms. For morbidity and health-related quality of life outcomes, in case of statistically significant and, if applicable, clinically relevant results of the primary analysis in which patients with a treatment switch or discontinuation were included as non-responders or with their last observed values (see Section 2.4.1.2), sensitivity analyses were used in which values of patients with treatment switch were not imputed. If the results were consistent, the certainty of conclusions of the results was not downgraded despite the high risk of bias.

This concurs with the assessment of the company insofar, as the company arrived at the same assessment of the risk of bias and also used sensitivity analyses for the assessment of the certainty of conclusions of the results for morbidity and health-related quality of life outcomes. However, the company based its assessment for side effect and mortality outcomes on a different date of analysis and on a different type of analysis (see Section 2.4.1.2).

Concurring with the assessment of the company, the risk of bias was rated as low for the results on the outcome "clinical remission", as the large proportion of patients with treatment switch or discontinuation can be addressed with an adequate imputation strategy for this outcome.

Detailed reasons for the assessment of the risk of bias can be found in Section 2.7.4.2 of the full dossier assessment.

2.4.2.3 Results

Table 14 and Table 15 summarize the results of the comparison of upadacitinib + MTX with adalimumab + MTX in adult patients for whom a first therapy with bDMARDs or tsDMARDs is indicated. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Tables on common AEs, SAEs and discontinuation due to AEs are presented in Appendix A.1 of the full dossier assessment. Furthermore, the results on DAS28 (CRP) ≤ 3.2 and DAS28 (erythrocyte sedimentation rate [ESR] ≤ 3.2 are presented as additional information in Appendix B.1 of the full dossier assessment.

Table 14: Results (all-cause mortality, morbidity, health-related quality of life and side effects, dichotomous) – RCT, direct comparison: upadacitinib + MTX vs. adalimumab + MTX (multipage table)

Study Outcome category Outcome Imputation strategy	Upadacitinib + MTX N	 Patients with event n (%)	Adalimumab + MTX N	 Patients with event n (%)	Upadacitinib + MTX vs. adalimumab + MTX RR [95% CI]; p-value
SELECT-COMPARE (analyses at week 26)					
Mortality					
All-cause mortality	650	0 (0)	327	2 (0.6)	–[a]; 0.046[b]
Morbidity					
Clinical remission[c]					
CDAI ≤ 2.8					
RNRI[d]	651	150 (23.0)	327	45 (13.8)	1.67 [1.23; 2.27]; 0.001[e]
SDAI ≤ 3.3					
RNRI[d]	651	158 (24.3)	327	45 (13.8)	1.75 [1.29; 2.38]; < 0.001[e]
Boolean definition					
RNRI[d]	651	117 (18.0)	327	32 (9.8)	1.84 [1.27; 2.65]; 0.001[e]
Low disease activity[c]					
CDAI ≤ 10					
RNRI[d]	651	343 (52.7)	327	125 (38.2)	1.38 [1.18; 1.61]; < 0.001[e]
Sensitivity analysis: NRI[f]	651	370 (56.8)	327	151 (46.2)	1.23 [1.08; 1.41]; 0.002[e]
SDAI ≤ 11					
RNRI[d]	651	351 (53.9)	327	127 (38.8)	1.39 [1.19; 1.62]; < 0.001[e]
Sensitivity analysis: NRI[f]	651	378 (58.1)	327	156 (47.7)	1.22 [1.07; 1.39]; 0.003[e]
Physical functioning (HAQ-DI)[g]					
RNRI[d]	651	398 (61.1)	327	173 (52.9)	1.15 [1.02; 1.30]; 0.021[e]
Sensitivity analysis: NRI[f]	651	480 (73.7)	327	234 (71.6)	1.03 [0.95; 1.12]; 0.492[e]
Fatigue (FACIT-Fatigue)[h]					
RNRI[d]	651	367 (56.4)	327	151 (46.2)	1.22 [1.07; 1.40]; 0.004[e]
Health-related quality of life					
SF-36v2[i]					
Physical Component Summary					
RNRI[d]	651	361 (55.5)	327	155 (47.4)	1.17 [1.02; 1.33]; 0.024[e]
Sensitivity analysis: NRI[f]	651	424 (65.1)	327	204 (62.4)	1.04 [0.94; 1.15]; 0.407[e]
Mental Component Summary					
RNRI[d]	651	262 (40.2)	327	110 (33.6)	1.19 [1.00; 1.43]; 0.052[e]

Table 14: Results (all-cause mortality, morbidity, health-related quality of life and side effects, dichotomous) – RCT, direct comparison: upadacitinib + MTX vs. adalimumab + MTX (multipage table)

Study Outcome category	Upadacitinib + MTX		Adalimumab + MTX		Upadacitinib + MTX vs. adalimumab + MTX
Outcome Imputation strategy	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Side effects					
AEs (supplementary information)	650	417 (64.2)	327	197 (60.2)	–
SAEs	650	24 (3.7)	327	14 (4.3)	0.86 [0.45; 1.64]; 0.736[b]
Discontinuation due to AEs	650	23 (3.5)	327	20 (6.1)	0.58 [0.32; 1.04]; 0.066[b]
Infections (SOC, AEs)	650	225 (34.6)	327	95 (29.1)	1.19 [0.98; 1.45]; 0.082[b]
Serious infections (SOC, SAEs)	650	12 (1.8)	327	5 (1.5)	1.21 [0.43; 3.40]; 0.791[b]

a. CI not interpretable.
b. Institute's calculation, unconditional exact test (CSZ method according to [16]).
c. The derivation of the added benefit is primarily based on the CDAI, see Section 2.7.4.3.2 of the full dossier assessment.
d. Primary analysis; patients with missing values at week 26 and patients with treatment switch before week 26 were rated as non-responders; values at a treatment switch at week 26 were imputed with the last value before the treatment switch.
e. Effect estimation based on a generalized linear model with treatment and stratification variable prior bDMARD treatment (yes, no) as covariables.
f. Patients with missing values at week 26 were rated as non-responders.
g. Patients with improvement by ≥ 0.22 points.
h. Patients with improvement by ≥ 4 points.
i. Patients with improvement by ≥ 5 points; only mean differences are available for the individual domains (physical functioning, physical role functioning, physical pain, general health perception, vitality, social functioning, emotional role functioning, mental wellbeing) (see Section 2.7.4.3.2 of the full dossier assessment).

AE: adverse event; bDMARD: biologic DMARD; CDAI: Clinical Disease Activity Index; CI: confidence interval; DMARD: disease-modifying antirheumatic drug; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; MTX: methotrexate; n: number of patients with (at least one) event; N: number of analysed patients; NRI: non-responder imputation; RCT: randomized controlled trial; RNRI: NRI after switch to rescue therapy; 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 and health-related quality of life, continuous) – RCT, direct comparison: upadacitinib + MTX vs. adalimumab + MTX (multipage table)

Study Outcome category Outcome Imputation strategy	Upadacitinib + MTX			Adalimumab + MTX			Upadacitinib + MTX vs. adalimumab + MTX
	N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)[b]	MD [95% CI]; p-value[b]
SELECT-COMPARE (analyses at week 26)							
Morbidity							
Tender joints[c]							
RLOCF[d]	604	15.1 (6.8)	−10.6 (0.4)	288	14.9 (6.9)	−9.0 (0.4)	−1.63 [−2.46; −0.81]; < 0.001
Sensitivity analysis: LOCF[e]	650	15.0 (6.9)	−11.5 (0.3)	323	15.1 (7.0)	−10.8 (0.3)	−0.65 [−1.29; −0.01]; 0.046
Swollen joints[c]							
RLOCF[d]	604	11.5 (5.6)	−8.4 (0.3)	288	11.5 (5.3)	−7.9 (0.4)	−0.48 [−1.13; 0.17]; 0.145
Pain (VAS)[f]							
RLOCF[d]	600	66.2 (20.8)	−36.8 (1.5)	287	66.6 (19.9)	−32.0 (1.8)	−4.88 [−8.28; −1.47]; 0.005 Hedges' g: −0.20 [−0.34; −0.06]
Patient assessment of disease activity (VAS)[f]							
RLOCF[d]	600	64.7 (21.9)	−35.3 (1.6)	287	66.4 (20.8)	−29.5 (1.8)	−5.76 [−9.19; −2.33]; 0.001 Hedges' g: −0.24 [−0.38; −0.09]
Morning stiffness[f]							
Severity (NRS)							
RLOCF[d]	602	6.3 (2.3)	−3.8 (0.2)	284	6.3 (2.1)	−3.3 (0.2)	−0.48 [−0.81; −0.16]; 0.004 Hedges' g: −0.21 [−0.35; −0.07]
Duration (min)							
RLOCF[d]	603	142.6 (185.8)	−100.5 (5.7)	285	149.2 (193.7)	−90.9 (6.8)	−9.57 [−22.16; 3.03]; 0.136
Health status (EQ-5D VAS)[g]							
RLOCF[d]	596	48.6 (23.2)	19.4 (1.4)	285	49.3 (22.1)	17.2 (1.7)	2.24 [−0.92; 5.39]; 0.165

Table 15: Results (morbidity and health-related quality of life, continuous) – RCT, direct comparison: upadacitinib + MTX vs. adalimumab + MTX (multipage table)

Study Outcome category Outcome Imputation strategy	Upadacitinib + MTX			Adalimumab + MTX			Upadacitinib + MTX vs. adalimumab + MTX
	N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)[b]	MD [95% CI]; p-value[b]
a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers. b. Effect estimation based on an analysis of covariance with treatment and stratification variable prior bDMARD treatment (yes, no) as fixed effects and baseline value as covariable. c. Based on 28 joints. d. Primary analysis; missing values and values after treatment switch are imputed with the last observed value. e. Missing values are imputed with the last observed value. f. A negative change from baseline to end of study indicates improvement; a negative effect estimation indicates an advantage for upadacitinib + MTX. g. A positive change from baseline to end of study indicates improvement; a positive effect estimation indicates an advantage for upadacitinib + MTX. bDMARD: biologic DMARD; CI: confidence interval; DMARD: disease-modifying antirheumatic drug; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; min: minutes; MTX: methotrexate; N: number of analysed patients; NRS: numeric rating scale; RCT: randomized controlled trial; RLOCF: rescue last observation carried forward; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus							

On the basis of the SELECT-COMPARE study, at most an indication, e.g. of an added benefit, can be derived for the outcome "clinical remission". For mortality and side effect outcomes, at most hints, e.g. of an added benefit or of greater or lesser harm, can be determined due to the high risk of bias. For outcomes on morbidity (except clinical remission) and health-related quality of life, at most hints, e.g. of an added benefit, can be initially determined due to the high risk of bias; the outcome-specific certainty of conclusions of the results may not be downgraded, however, so that at most indications can be derived (see Section 2.4.2.2).

Mortality

All-cause mortality

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome „all-cause mortality". This resulted in a hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX.

This deviates from the approach of the company, which used event time analyses at week 48 for the derivation of all-cause mortality, and derived no added benefit on the basis of these data.

Morbidity

Clinical remission

The outcome "clinical remission" was operationalized using the CDAI ≤ 2.8, the SDAI ≤ 3.3, or the Boolean definition according to ACR/EULAR. The assessment of clinical remission was primarily based on the CDAI ≤ 2.8.

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome „clinical remission" based on the CDAI ≤ 2.8. This resulted in an indication of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX. This effect was confirmed by the results of the operationalizations SDAI ≤ 3.3 and Boolean definition.

This concurs with the assessment of the company, which did not primarily use the CDAI ≤ 2.8 for its assessment, however, but considered CDAI ≤ 2.8, SDAI ≤ 3.3 and Boolean definition in the overall consideration.

Low disease activity

The outcome "low disease activity" was operationalized as reaching the criteria of CDAI ≤ 10 and SDAI ≤ 11. The assessment of low disease activity was primarily based on the CDAI ≤ 10.

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome „low disease activity" based on the CDAI ≤ 10. Since the sensitivity analysis without imputation of patients with treatment switch confirmed this effect regarding statistical significance, there was an indication of an added benefit of upadacitinib + MTX versus adalimumab + MTX despite the high risk of bias. This effect was confirmed by the results of the SDAI ≤ 11.

This concurs with the assessment of the company, which did not primarily use the CDAI ≤ 10 for its assessment, however, but considered CDAI ≤ 10, SDAI ≤ 11, as well as DAS28 (CRP) ≤ 3.2 and DAS28 (ESR) ≤ 3.2 in the overall consideration.

Tender joints

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome "tender joints" based on the mean differences. The corresponding 95% CI of the mean difference included a difference of < 1 joint. It can therefore not be inferred that the effect was relevant. This was confirmed in the sensitivity analysis. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

This deviates from the approach of the company, which considered the tender and swollen joint count together and derived an indication of an added benefit on the basis of the response criterion of a maximum of 1 tender (or swollen) joint.

Swollen joints

For the outcome "swollen joints", no statistically significant difference between the treatment groups was shown based on the mean differences. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

This deviates from the approach of the company, which considered the tender and swollen joint count together and derived an indication of an added benefit on the basis of the response criterion of a maximum of 1 swollen (or tender) joint.

Pain (VAS)

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome "pain (VAS)". The SMD in the form of Hedges' g was considered to check the relevance of the result. However, the 95% CI of the SMD was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect was relevant. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

This deviates from the approach of the company, which derived an indication of an added benefit on the basis of analyses on a response criterion (primary analysis and sensitivity analysis).

Patient assessment of disease activity (VAS)

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome "patient assessment of disease activity (VAS)". The SMD in the form of Hedges' g was considered to check the relevance of the result. However, the 95% CI was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect was relevant. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

This concurs with the company's assessment.

Physical functioning (HAQ-DI)

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome "physical functioning (HAQ-DI)". Since the sensitivity analysis did not confirm this effect regarding statistical significance, there was a hint of an added benefit of upadacitinib + MTX versus adalimumab + MTX due to the high risk of bias.

This concurs with the company's assessment.

Fatigue (FACIT-Fatigue)

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome "fatigue (FACIT-Fatigue)". The extent of the effect was no more than marginal,

however. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived a hint of an added benefit for this outcome.

Morning stiffness (severity [NRS], duration)

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome "severity (NRS) of morning stiffness". The SMD in the form of Hedges' g was considered to check the relevance of the result. However, the 95% CI of the SMD was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect was relevant. There was no statistically significant difference between the treatment groups for the duration of morning stiffness. This did not result in a hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX for the severity (NRS) or for the duration of morning stiffness; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for the outcome "health status" (EQ-5D VAS). This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

SF-36v2 – Physical and Mental Component Summary

A statistically significant difference in favour of upadacitinib + MTX was shown for the Physical Component Summary of the SF-36v2. Since the sensitivity analysis did not confirm this effect regarding statistical significance, there was a hint of an added benefit of upadacitinib + MTX versus adalimumab + MTX due to the high risk of bias.

No statistically significant difference between the treatment groups was shown for the Mental Component Summary of the SF-36v2. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

This concurs with the assessment of the company both for the Physical and for the Mental Component Summary of the SF-36v2.

Side effects

SAEs, discontinuation due to AEs

No statistically significant differences were shown between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". In each case, this resulted in no hint of greater or lesser harm from upadacitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven for each of these outcomes.

For both outcomes, this concurs with the assessment of the company, which based its assessment on the event time analyses at week 48, however.

Infections, serious infections

No statistically significant differences between the treatment groups were shown for the outcomes "infections" and "serious infections". In each case, this resulted in no hint of greater or lesser harm from upadacitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven for each of these outcomes.

This deviates from the approach of the company, which did not consider the 2 outcomes, operationalized with the SOC "infections and infestations", in its assessment, but a different operationalization for infections (Custom MedDRA Query [CMQ]). However, the company did not derive greater or lesser harm from upadacitinib on the basis of this operationalization.

2.4.2.4 Subgroups and other effect modifiers

For the present assessment, the following predefined subgroup characteristics were used for adult patients for whom a first therapy with bDMARDs or tsDMARDs is indicated:

- age (< 40 years, ≥ 40 to < 65 years, ≥ 65 years)
- sex (female, male)
- geographical region (North America, South/Central America, Eastern Europe, Western Europe, Asia, other)
- disease activity at baseline based on the DAS28 (CRP) (DAS28 [CRP] ≤ 5.1 [no high disease activity], DAS28 [CRP] > 5.1 [high disease activity]

For the analysis date relevant for the benefit assessment (week 26), the company presented subgroup analyses only for the outcome categories of morbidity and health-related quality of life. For the outcomes "tender joints" and "swollen joints", the company only presented subgroup analyses on the basis of the response criterion of at most 1 tender or swollen joint. These analyses were not used for the present benefit assessment (see Section 2.7.4.3.2 of the full dossier assessment for reasons).

For side effect outcomes and the outcome "all-cause mortality", the company only presented event time analyses at week 48 for subgroups. These analyses were also not used for the present benefit assessment (see Section 2.7.4.1 of the full dossier assessment for reasons).

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there must be 10 events in at least one subgroup.

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

There was no relevant effect modification for any of the available subgroup analyses on morbidity and health-related quality of life outcomes.

2.4.3 Probability and extent of added benefit

Probability and extent of added benefit for adult patients for whom a first therapy with bDMARDs or tsDMARDs is indicated are derived at outcome level below, 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 the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.4.2 (see Table 16).

Determination of the outcome category for symptom outcomes

The dossier does not provide information for every outcome considered in the present benefit assessment whether it was serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Clinical remission, low disease activity and physical functioning (HAQ-DI)

Concurring with the company, the outcomes “clinical remission” and “low disease activity” are allocated to the outcome category of serious/severe symptoms/late complications, as it can be assumed on the basis of the information on disease activity at baseline that the majority of the patients had serious/severe symptoms at this time point (see Table 10). Concurring with the company, the outcome “physical functioning (HAQ-DI)” is allocated to the outcome category of serious/severe symptoms/late complications, as, based on the citation provided by the company, Marra 2005 [17], on average, the patients presented with severe limitation of physical functioning at baseline (see Table 10).

Fatigue (FACIT-Fatigue)

The company allocated the outcome “fatigue (FACIT-Fatigue)” to the outcome category of serious/severe symptoms/late complications. It justified this by stating that the patients in both

treatment arms, on average, were within the threshold of severe fatigue (≤ 35 points) defined for patients with rheumatoid arthritis, measured using the SF-36v2 vitality scale [18]. According to the company, the SF-36v2 vitality scale in turn shows close association with the FACIT-Fatigue [19]. This rationale is not appropriate. The threshold value used by the company is not an established threshold value for the severity classification of fatigue for the FACIT-Fatigue. A threshold value for this scale is necessary to assess the severity of the fatigue recorded with the FACIT-Fatigue. Furthermore, the study documents show that patients in both treatment arms had a mean baseline value of about 40 points on the SF-36v2 vitality scale, for which the company specified a threshold value. Thus, the patients were above the threshold value of severe fatigue of ≤ 35 points cited by the company. Deviating from the company, the outcome “fatigue” (recorded with the FACIT-Fatigue) is therefore allocated to the outcome category of non-serious/non-severe symptoms/late complications.

Table 16: Extent of added benefit at outcome level: upadacitinib + MTX vs. adalimumab + MTX (multipage table)

Outcome category **Outcome**	**Upadacitinib + MTX vs. adalimumab + MTX** **Proportion of events (%) or mean change** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0.6% RR: –[c]; p = 0.046 probability: „hint"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "non-quantifiable"
Morbidity		
Clinical remission (CDAI ≤ 2.8)	23.0% vs. 13.8% RR: 1.67 [1.23; 2.27]; p = 0.001 RR[d]: 0.60 [0.44; 0.81] probability: „indication"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "considerable"
Low disease activity (CDAI ≤ 10)	52.7% vs. 38.2% RR: 1.38 [1.18; 1.61]; p < 0.001 RR[d]: 0.72 [0.62; 0.85] probability: „indication"	Outcome category: serious/severe symptoms/late complications added benefit, extent: „non-quantifiable"[e]
Tender joints[f]	Mean change: −10.6 vs. −9.0 MD: −1.63 [−2.46, −0.81][g]; p < 0.001	Lesser benefit/added benefit not proven
Swollen joints[f]	Mean change: −8.4 vs. −7.9 MD: −0.48 [−1.13; 0.17]; p = 0.145	Lesser benefit/added benefit not proven
Pain (VAS)	Mean change: −36.8 vs. −32.0 MD: −4.88 [−8.28; −1.47]; p = 0.005 Hedges' g: −0.20 [−0.34; −0.06][h]	Lesser benefit/added benefit not proven
Patient assessment of disease activity (VAS)	Mean change: −35.3 vs. −29.5 MD: −5.76 [−9.19; −2.33]; p = 0.001 Hedges' g: −0.24 [−0.38; −0.09][h]	Lesser benefit/added benefit not proven
Physical functioning (HAQ-DI)[i]	61.1% vs. 52.9% RR: 1.15 [1.02; 1.30]; p = 0.021 RR[d]: 0.87 [0.77; 0.98] probability: „hint"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "minor"
Fatigue (FACIT-Fatigue)[j]	56.4% vs. 46.2% RR: 1.22 [1.07; 1.40]; p = 0.004 RR[d]: 0.82 [0.71; 0.93]	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[k]

Table 16: Extent of added benefit at outcome level: upadacitinib + MTX vs. adalimumab + MTX (multipage table)

Outcome category **Outcome**	**Upadacitinib + MTX vs. adalimumab + MTX** **Proportion of events (%) or mean change** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Morning stiffness		
Severity (NRS)	Mean change: −3.8 vs. −3.3 MD: −0.48 [−0.81; −0.16]; p = 0.004 Hedges' g: −0.21 [−0.35; −0.07][h]	Lesser benefit/added benefit not proven
Duration (min)	Mean change: −100.5 vs. −90.9 MD: −9.57 [−22.16; 3.03]; p = 0.136	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	Mean change: 19.4 vs. 17.2 MD: 2.24 [−0.92; 5.39]; p = 0.165	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36v2[l]		
Physical Component Summary	55.5% vs. 47.4% RR: 1.17 [1.02; 1.33]; p = 0.024 RR[d]: 0.85 [0.75; 0.98] probability: „hint"	Outcome category: health-related quality of life added benefit, extent: "minor"
Mental Component Summary	40.2% vs. 33.6% RR: 1.19 [1.00; 1.43]; p = 0.052	Lesser benefit/added benefit not proven
Side effects		
SAEs	3.7% vs. 4.3% RR: 0.86 [0.45; 1.64]; p = 0.736	Greater/lesser harm not proven
Discontinuation due to AEs	3.5% vs. 6.1% RR: 0.58 [0.32; 1.04]; p = 0.066	Greater/lesser harm not proven
Infections (SOC, AEs)	34.6% vs. 29.1% RR: 1.19 [0.98; 1.45]; p = 0.082	Greater/lesser harm not proven
Serious infections (SOC, SAEs)	1.8% vs. 1.5% RR: 1.21 [0.43; 3.40]; p = 0.791	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. CI not interpretable.
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e. Extent non-quantifiable, as the primary analysis and the sensitivity analysis produce different conclusions regarding the extent.
f. Based on 28 joints.
g. Since the CI includes a difference of < 1 joint, it cannot be inferred that there is a relevant effect.
h. 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, the presence of a relevant effect cannot be inferred.
i. Patients with improvement by ≥ 0.22 points.

Table 16: Extent of added benefit at outcome level: upadacitinib + MTX vs. adalimumab + MTX (multipage table)

Outcome category **Outcome**	**Upadacitinib + MTX vs. adalimumab + MTX** **Proportion of events (%) or mean change** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
j. Patients with improvement by ≥ 4 points. k. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. i. Patients with improvement by ≥ 5 points. AE: adverse event; CDAI: Clinical Disease Activity Index; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; MD: mean difference; min: minute; MTX: methotrexate; NRS: numeric rating scale; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus		

2.4.3.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 17: Positive and negative effects from the assessment of upadacitinib + MTX in comparison with adalimumab + MTX

Positive effects	**Negative effects**
Mortality ▪ All-cause mortality hint of an added benefit – extent: "non-quantifiable"	–
Serious/severe symptoms/late complications ▪ Clinical remission (CDAI ≤ 2.8) indication of an added benefit – extent: "considerable" ▪ Low disease activity (CDAI ≤ 10) indication of an added benefit – extent: "non-quantifiable" ▪ Physical functioning (HAQ-DI) hint of an added benefit – extent: "minor"	
Health-related quality of life ▪ SF-36v2 ▫ Physical Component Summary: hint of an added benefit – extent: "minor"	
For research question 2, only data are available for the subpopulation of patients for whom a combination therapy with MTX is an option. No data are available for patients for whom monotherapy with upadacitinib is an option.	
CDAI: Clinical Disease Activity Index; HAQ-DI: Health Assessment Questionnaire-Disability Index; MTX: methotrexate; SF-36v2: Short Form (36) – version 2 Health Survey	

In the overall consideration, there were exclusively positive effects of upadacitinib + MTX in comparison with adalimumab + MTX for adult patients for whom a first therapy with bDMARDs or tsDMARDs is indicated. This concerns outcomes of all outcome categories except side effects. Indications of an added benefit were shown for clinical remission and low disease activity, the key outcomes in the therapeutic indication. In case of clinical remission, which is the primary treatment goal in this therapeutic indication, the extent of the added benefit can be quantified as "considerable". For the outcome "low disease activity", the extent is non-quantifiable, as the primary analysis and the sensitivity analysis produce different conclusions regarding the extent. In addition, there were several hints of a minor added benefit, e.g. also for health-related quality of life. Since the positive effects were not accompanied by negative effects, this resulted overall in an indication of considerable added benefit.

In summary, there is an indication of considerable added benefit of upadacitinib + MTX versus adalimumab + MTX for adult patients with moderate to severe active rheumatoid arthritis for whom a first therapy with bDMARDs or tsDMARDs is indicated.

No data are available for the patient group for whom monotherapy with upadacitinib is an option. The added benefit is not proven for this patient group.

The assessment described above deviates from that of the company insofar as the company also derived an indication of considerable added benefit, but did not differentiate between the patient groups for whom a combination therapy of upadacitinib + MTX or monotherapy with upadacitinib is an option.

2.5 Research question 3: adult patients with inadequate response or intolerance to pretreatment with one or more bDMARDs and/or tsDMARDs

2.5.1 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 upadacitinib (status: 2 December 2019)
- bibliographical literature search on upadacitinib (last search on 5 November 2019)
- search in trial registries for studies on upadacitinib (last search on 5 November 2019)

To check the completeness of the study pool:

- search in trial registries for studies on upadacitinib (last search on 22 January 2020)

No additional relevant study was identified from the check.

2.5.1.1 Studies included

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

Table 18: Study pool – RCT, direct comparison: upadacitinib + MTX vs. abatacept + MTX

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and sources on the G-BA website (yes/no [citation])
M15-925 (SELECT CHOICE[c])	Yes	Yes	No	Yes [20,21]	Yes [22,23]	No

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c: In the following tables, the study is referred to with this designation.

CSR: clinical study report; G-BA: Federal Joint Committee; MTX: methotrexate; RCT: randomized controlled trial; vs.: versus

The study pool of the benefit assessment of upadacitinib in comparison with the ACT for research question 3 consisted of the RCT SELECT-CHOICE and corresponded to the study pool of the company. The study compared upadacitinib + csDMARDs with abatacept + csDMARDs. The SELECT-CHOICE study is exclusively suitable to derive conclusions on the added benefit of upadacitinib for the combination therapy with MTX, based on a subpopulation (see also Section 2.5.1.2).

2.5.1.2 Study characteristics

Table 19 and Table 20 describe the study used for the benefit assessment.

Table 19: Characteristics of the study included – RCT, direct comparison: upadacitinib + MTX vs. abatacept + MTX

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
SELECT-CHOICE	RCT, double-blind, parallel	Patients ≥ 18 years with moderate to severe active rheumatoid arthritis ▪ after inadequate response to pretreatment with ≥ 1 bDMARD for ≥ 3 months or discontinuation of pretreatment due to intolerability/toxicity ▪ with pretreatment with csDMARD(s)b for ≥ 3 months and on a stable dose for ≥ 4 weeks prior to the first dose of study medication	Upadacitinib + csDMARD(s) (N = 304[c]) abatacept + csDMARD(s) (N = 309[c]) Relevant subpopulation thereof: upadacitinib + MTX (n = 223) abatacept + MTX (n = 215)	Screening: 35 days Period 1: ▪ double-blind treatment for 24 weeks[d] Period 2: ▪ open-label extension phase for up to 5 years Follow-up observation[e]: ▪ until 70 days after the last dose of the study medication	119 centres in 27 countries[f] 5/2017–ongoing Data cut-off at week 24: 3 September 2019	Primary: ▪ change in DAS28 (CRP) at week 12 Secondary: ▪ morbidity ▪ health-related quality of life ▪ AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Allowed csDMARDs: MTX, sulfasalazine, hydroxychloroquine, chloroquine or leflunomide, as well as combination of ≤ 2 csDMARDs (except the combination of MTX and leflunomide).
c. Only patients recruited as of protocol amendment 4 from 12 October 2017 were considered. Patients randomized before that date (N = 44), in the intervention arm, received a dosage of 30 mg upadacitinib once daily, which is not in compliance with the approval. In the analyses, these 44 patients were neither considered in the upadacitinib arm nor in the abatacept arm.
d. Patients allocated to abatacept were switched to treatment with upadacitinib after week 24.
e. Outcome-specific information is provided in Table 21.
f. Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Czech Republic, Germany, Greece, Hungary, Israel, Italy, Latvia, Mexico, Netherlands, New Zealand, Poland, Portugal, Romania, Russia, South Korea, Spain, Sweden, Switzerland, Turkey, United Kingdom, USA; information from the study documents (Module 4 provides contradictory information on the number of centres and countries).

AE: adverse event; bDMARD: biologic DMARD; CRP: C-reactive protein; csDMARD: conventional synthetic DMARD; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial

Table 20: Characteristics of the intervention – RCT, direct comparison: upadacitinib + MTX vs. abatacept + MTX

Study	Intervention	Comparison
SELECT-CHOICE	Upadacitinib 15 mg orally, once/day[a] + placebo IV, day 1, weeks 2, 4, 8, 12, 16 and 20	Abatacept in weight-dependent dosage[b], IV, day 1, weeks 2, 4, 8, 12, 16 and 20[a] + placebo orally, once/day
	Allowed prior and concomitant treatment ▪ csDMARD(s) (incl. MTX): pretreatment with csDMARD(s) ≥ 3 months; continuation of therapy that has been ongoing for ≥ 4 weeks on a stable dose[c, d] ▪ folic acid/folinic acid supplementation in case of concomitant treatment with MTX ▪ NSAID, paracetamol on a stable dose ≥ 1 week before the first dose of the study medication[d] ▪ oral corticosteroids (≤ 10 mg prednisone or equivalent daily) or inhaled corticosteroids on a stable dose ≥ 4 weeks before first dose of the study medication[d, e] ▪ corticosteroids (IA, IM, IV, etc.): injections as treatment adjustment in case of inadequate response allowed from week 12[f] ▪ bDMARDs: pretreatment with ≥ 1 bDMARD for ≥ 3 months in case of inadequate response or discontinuation due to intolerability/toxicity[g] **Non-permitted pretreatment** ▪ abatacept ▪ JAK inhibitors **Non-permitted concomitant treatment** ▪ bDMARDs[g] ▪ strong opiates (e.g. oxycodone, morphine) ▪ strong CYP3A inhibitors or inducers ▪ traditional Chinese drugs ▪ live vaccines	

a. Patients with inadequate response received the following treatment adjustments:
- Patients with < 20% improvement in swollen and tender joint count compared with baseline on 2 consecutive visits from week 12 received optimized concomitant treatment according to local requirements (optimization of treatment with csDMARDs [≤ 2 csDMARDs, except combination of MTX and leflunomide]), NSAIDs, paracetamol, corticosteroids or weak analgesics including addition of new drugs).
- Patients with deterioration in swollen or tender joint count compared with baseline on 2 consecutive visits from week 12 had to discontinue the study medication and received standard therapy of physician's choice.

b. Depending on body weight: < 60 kg: 500 mg, 60–100 kg: 750 mg, > 100 kg: 1000 mg.
c. Permitted csDMARDs: oral or parenteral MTX (7.5–25 mg/week), sulfasalazine (≤ 3000 mg/day), hydroxychloroquine (≤ 400 mg/day), chloroquine (≤ 250 mg/day) or leflunomide (≤ 20 mg/day); simultaneous administration of ≤ 2 csDMARDs (except combination of MTX and leflunomide).
d. As of week 12, adjustments according to local requirements as therapy adjustment were allowed in case of inadequate response.
e. High-dose corticosteroids (prednisone equivalent ≤ 0.5 mg/kg body weight/day) were allowed for a maximum of 3 days as therapy adjustment in case of inadequate response as of week 12.
f. Not permitted within 8 weeks before the first dose of the study medication until week 12; after week 12, to be avoided within 21 days before a study visit, joints were rated as "not assessable" for 3 months after injection.
g. bDMARDs had to be discontinued at least 4 weeks before the first dose of the study medication.

bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; CYP3A: cytochrome P450 3A; DMARD: disease-modifying antirheumatic drug; IA: intraarticular; IM: intramuscular; IV: intravenous; JAK: Janus kinase; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; vs.: versus

The SELECT-CHOICE study is randomized, double-blind study on the comparison of upadacitinib with abatacept, each in combination with csDMARD treatment.

The study included adult patients with moderate to severe active rheumatoid arthritis who had responded inadequately to, or had not tolerated, pretreatment of at least 3 months with ≥ 1 bDMARD (except abatacept). In addition, the patients had been receiving csDMARD(s) on a stable dose within the last 4 weeks before the first dose of the study medication and had to continue this therapy as concomitant treatment during the study.

Diagnosis of rheumatoid arthritis had to be conducted at least 3 months earlier and according to the 2010 ACR/EULAR classification criteria [11]. In addition, patients had to fulfil the following criteria to be eligible for enrolment:

- ≥ 6 swollen and ≥ 6 tender joints, based on 66 or 68 joint counts respectively
- a CRP value of ≥ 3 mg/L

A total of 657 patients were randomly allocated in a 1:1 ratio to upadacitinib + csDMARD(s) (N = 304) and abatacept + csDMARD(s) (N = 309). In addition to bDMARD pretreatment (failure to 1 or 2 bDMARDs with the same mechanism of action/failure to different mechanisms of action or ≥ 3 bDMARDs with the same mechanism of action), stratification was by geographic region.

Patients randomized up to and including protocol amendment 3 received 30 mg upadacitinib once/day, a dosage that is not in compliance with the approval, in the intervention arm. These patients were therefore not considered in the analyses. This concerned 21 patients in the upadacitinib arm and 23 patients in the abatacept arm. Patients randomized as of protocol amendment 4 received treatment with upadacitinib in compliance with the SPC [13]. Treatment with abatacept was also in compliance with the corresponding SPC [24].

During the study, from week 12, predefined therapy adjustments were made if certain criteria for response to treatment were not met. Patients with < 20% improvement in swollen and tender joint count in comparison with baseline on 2 consecutive visits from week 12 received optimized concomitant treatment according to local requirements. The options of this concomitant treatment were initiation or optimization of treatment with NSAIDs and corticosteroids, but also optimized treatment with csDMARDs, whereby a maximum of 2 csDMARDs, except for the combination of MTX and leflunomide, could be administered simultaneously. Treatment switch in the respective other study arm was not planned in the SELECT-CHOICE study.

Patients with deterioration in swollen or tender joint count compared with baseline on 2 consecutive visits from week 12 had to discontinue the study medication and received standard therapy of physician's choice. The company did not provide any information on the number of patients in the relevant subpopulation (see below) whose treatment had to be

discontinued due to lack of efficacy. It can be inferred from the study documents that only few patients in the total population discontinued treatment for this reason.

The planned double-blind, randomized treatment phase of the SELECT-CHOICE study was 24 weeks. In the subsequent extension phase, which is still ongoing, all patients were switched to open-label treatment with upadacitinib. Analyses at the end of the randomized treatment phase of 24 weeks are available for the study.

Primary outcome of the study is the change in DAS28 (CRP) at week 12. Patient-relevant outcomes on morbidity, health-related quality of life and AEs were additionally recorded.

Relevant subpopulation for research question 3

In the SELECT-CHOICE study, the csDMARD treatment administered on a stable dose within the last 4 weeks before study inclusion was continued. The concomitant treatment with csDMARDs allowed in the study was in compliance with the approval only for a subpopulation of the study, as upadacitinib is approved only in combination with MTX or as monotherapy [13], and abatacept only in combination with MTX [24]. Treatment with other csDMARD(s) without MTX and the combination therapy with MTX and further additional csDMARD(s) do not comply with the recommendations of the SPCs of upadacitinib and abatacept. Thus, only the subpopulation who received treatment with upadacitinib or abatacept, each in combination with MTX, was relevant for the present benefit assessment. These were 223 patients in the intervention arm and 215 patients in the comparator arm.

During the study, from week 12, predefined therapy adjustments were made if certain criteria for response to treatment were not met (see above). The company did not present any information for the relevant subpopulation as to how many patients received additional csDMARDs as therapy adjustment from week 12. It can be inferred from the information on the total population that such an adjustment was only performed in few patients, however. It was therefore assumed for the present benefit assessment that the majority of the patients in the relevant subpopulation received treatment in compliance with the approval of upadacitinib and abatacept also in the course of the study.

Table 21 shows the planned duration of follow-up observation of the patients for the different outcome categories in the double-blind treatment phase until week 24. The planned duration of the follow-up observation in the extension phase is not presented, as this phase is not relevant in the present situation (see above).

Table 21: Planned duration of follow-up observation (double-blind treatment phase [24 weeks]) – RCT, direct comparison: upadacitinib + MTX vs. abatacept + MTX

Study **Outcome category** **Outcome**	**Planned follow-up observation**
SELECT-CHOICE	
Mortality	
All-cause mortality	See information on the outcome category of side effects
Morbidity	
All outcomes in the category of morbidity	▪ In case of premature study discontinuation: study visit within 2 weeks ▪ After end of therapy: no follow-up planned
Health-related quality of life	
SF-36v2	▪ In case of premature study discontinuation: study visit within 2 weeks ▪ After end of therapy: no follow-up planned
Side effects	
All outcomes in the category of side effects	▪ After completion of 24 weeks under study medication and subsequent participation in the open-label extension phase: no follow-up planned ▪ After completion of 24 weeks under study medication without subsequent participation in the open-label extension phase: ▫ 30 days of follow-up after the last administration of the study medication ▫ 70 days of follow-up after the last administration of the study medication[a] ▪ In case of premature treatment discontinuation and continued study participation: study visit within 2 weeks, then[b]: ▫ 30 days of follow-up after the last administration of the study medication ▫ 70 days of follow-up after the last administration of the study medication[a] ▪ In case of premature study discontinuation: study visit within 2 weeks, then: ▫ optional 30 days of follow-up after the last administration of the study medication ▫ optional 70 days of follow-up after the last administration of the study medication[a]

a. It is not clear from the available data whether or not the duration of follow-up observation was different for the 2 treatment arms, as there was discrepant information.
b. Not applicable to patients with regular study visit in the double-blind treatment phase at this time point.

MTX: methotrexate; RCT: randomized controlled trial; SF-36v2: Short Form (36) – version 2 Health Survey; vs.: versus

No follow-up observation after the end of therapy was planned for outcomes on morbidity and health-related quality of life. In case of premature study discontinuation, a follow-up visit took place within 2 weeks after the last dose of the study medication. It can be assumed that the duration of follow-up observation for the outcomes of the categories of mortality and side effects for patients with premature treatment discontinuation and for patients who ended the study after completion of the double-blind phase of 24 weeks differed under certain conditions for the 2 study arms: 30 days in the intervention arm and 70 days in the comparator arm. This was not clear from the study documents, however. Assuming different follow-up observation for patients in the intervention and in the comparator arm, these differences in follow-up

observation are reduced by 4 weeks, as the last administration of abatacept was already at week 20, whereas upadacitinib in the double-blind phase was last given at week 24. The difference in follow-up observation was thus effectively 12 days instead of 40 days. It can be inferred from the information on the total population of the study that a majority of the patients continued the study in the open-label extension phase after completion of the double-blind phase (about 90%). In this case, no different follow-up observation of AEs was planned. The company did not provide any information on the number of patients in the relevant subpopulation for whom follow-up observation was actually different. This was considered in the assessment of the risk of bias (see Section 2.5.2.2).

Types of analysis

In the SELECT-CHOICE study, it was planned as primary analysis for binary variables to impute patients with missing values at the date of analysis as non-responders by means of NRI. It was planned as primary analysis for primary variables with continuous analysis to impute patients with missing values by means of multiple imputation (MI). Analyses that only consider actually observed values without imputation of missing values were planned as sensitivity analysis for primary variables in the SELECT-CHOICE study. Analyses that only consider actually observed values without imputation of missing values were planned for secondary and exploratory variables. Only analyses on the basis of naive rates were planned for AEs in the SELECT-CHOICE study.

For binary variables, the company used the primarily planned NRI analyses for the SELECT-CHOICE study. For continuous variables, the company mainly used the MI analyses primarily planned in the study for primary variables with continuous analysis. Exceptions were the outcomes "swollen and tender joints", for which, according to the study documents only analyses without imputation of missing values were planned. For these outcomes, the company presented analyses in which patients were included with their last observed values (LOCF imputation). The company did not consider sensitivity analyses for the SELECT-CHOICE study.

Concurring with the company, the analyses primarily planned in the study were used for the present benefit assessment. For the outcomes "swollen and tender joints", the analyses with LOCF imputation presented by the company were used. Deviating from the company, for outcomes with high risk of bias due to a large proportion of imputed values, sensitivity analyses with alternative imputation strategies were used for the SELECT-CHOICE study to check whether the certainty of conclusions of the results had to be downgraded due to the high risk of bias. Such sensitivity analyses on the basis of calculations conducted by the Institute were only performed for outcomes for which there were statistically significant and clinically relevant results besides a high risk of bias (see also Sections 2.7.4.1 and 2.7.4.2 of the full dossier assessment). See Sections 2.5.2.4 and 2.5.3.2 for information on the concrete approach used in these outcomes.

Patient characteristics

Table 22 shows the characteristics of the patients in the study included.

Table 22: Characteristics of the study population – RCT, direct comparison: upadacitinib + MTX vs. abatacept + MTX (multipage table)

Study Characteristics Category	Upadacitinib + MTX N[a] = 223	Abatacept + MTX N[a] = 215
SELECT-CHOICE		
Age [years], mean (SD)	56 (11)	56 (12)
Sex [F/M], %	83/17	81/19
Region, n (%)		
North America	49 (22)	44 (21)
South/Middle America	71 (32)	65 (30)
Eastern Europe	62 (28)	67 (31)
Western Europe	31 (14)	31 (14)
Asia	3 (1)	2 (1)
Other	7 (3)	6 (3)
Disease duration: time between first diagnosis and randomization [years], median [Q1; Q3]	10.2 [5.2; 17.1]	10.5 [4.6; 15.7]
Rheumatoid factor status, n (%)		
Positive	154 (69)	155 (72)
Negative	69 (31)	60 (28)
Anti-CCP, n (%)		
Positive	163 (73)	159 (74)
Negative	59 (26)	56 (26)
Unknown	1 (0)	0 (0)
DAS28 (CRP), (disease activity at baseline), mean (SD)	5.7 (0.9)	5.9 (1.0)
DAS28 (CRP), (disease activity at baseline), n (%)		
≤ 5.1	59 (26)	46 (21)
> 5.1	164 (74)	168 (78)
Unknown	0 (0)	1 (0)
Tender joint count[b], mean (SD)	14.5 (6.3)	15.8 (6.7)
Swollen joint count[b], mean (SD)	10.4 (4.7)	11.5 (5.2)
Functional status [HAQ-DI], mean (SD)	1.7 (0.6)	1.7 (0.6)
Pretreatment		
Number of bDMARDs, n (%)		
1	147 (66)	142 (66)
2	47 (21)	47 (22)
≥ 3	25 (11)	24 (11)
Unknown	4 (2)	2 (1)
Treatment failure to ≥ 1 TNF alpha inhibitor, n (%)	195 (87)	191 (89)
Treatment failure to ≥ 1 IL6 inhibitor, n (%)	37 (17)	35 (16)
Treatment discontinuation[c], n (%)	ND	ND
Study discontinuation[c], n (%)	ND	ND

Table 22: Characteristics of the study population – RCT, direct comparison: upadacitinib + MTX vs. abatacept + MTX (multipage table)

Study Characteristics Category	Upadacitinib + MTX N[a] = 223	Abatacept + MTX N[a] = 215

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Based on 28 joints.
c. The company presented information on the proportion of patients with treatment or study discontinuation only for the total population of the study and not for the relevant subpopulation. In the total population, 30 patients (10%) in the upadacitinib arm and 33 patients (11%) in the abatacept arm discontinued treatment. In the total population, 24 patients (8%) in the upadacitinib arm and 32 patients (10%) in the abatacept arm discontinued the study.

bDMARD: biologic DMARD; CCP: cyclic citrullinated peptide; CRP: C-reactive protein; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; DMARD: disease-modifying antirheumatic drug; F: female; HAQ-DI: Health Assessment Questionnaire-Disability Index; IL6: interleukin-6; M: male; MTX: methotrexate; n: number of patients in the respective category; N: number of patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; TNF: tumour necrosis factor; vs.: versus

The demographic and clinical characteristics between the 2 arms of the SELECT-CHOICE study were sufficiently balanced. The mean age of the patients was about 56 years, and most of them were women (about 80%). About 3 quarters of the patients had high disease activity at baseline (defined as DAS28 [CRP] > 5.1). The mean swollen joint count was about 11 of 28 joints, and the majority of the patients had further poor prognostic factors, such as a positive rheumatoid factor or anti-CCP antibody status. About 66% of the patients had been pretreated with one bDMARD, the other patients with ≥ 2 bDMARDs. The company did not present information on the proportion of patients with treatment or study discontinuation for the relevant subpopulation.

Risk of bias across outcomes (study level)

Table 23 shows the risk of bias across outcomes (risk of bias at study level).

Table 23: Risk of bias across outcomes (study level) – RCT, direct comparison: upadacitinib + MTX vs. abatacept + MTX

Study	Adequate random sequence generation	Allocation concealment	Blinding: Patients	Blinding: Treating staff	Reporting independent of the results	No additional aspects	Risk of bias at study level
SELECT-CHOICE	Yes	Yes	Yes	Yes	Yes	Yes	Low

MTX: methotrexate; RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as low for the SELECT-CHOICE study. This concurs with the company's assessment.

2.5.2 Results on added benefit

2.5.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

- Mortality
  - all-cause mortality
- morbidity
  - clinical remission
  - low disease activity
  - tender joints
  - swollen joints
  - pain (recorded using a VAS)
  - patient assessment of disease activity (recorded using a VAS)
  - physical functioning (recorded using the HAQ-DI)
  - fatigue (recorded using the FACIT-Fatigue)
  - morning stiffness (severity [recorded using an NRS], duration)
  - health status (recorded using the EQ-5D VAS)
- Health-related quality of life
  - recorded using the Physical and Mental Component Summary of the SF-36v2
- Side effects
  - SAEs
  - discontinuation due to AEs
  - infections (SOC “infections and infestations”, AEs)
  - serious infections (SOC “infections and infestations”, SAEs)
  - 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) (see Section 2.7.4.3.2 of the full dossier assessment).

Table 24 shows for which outcomes data were available in the study included.

Table 24: Matrix of outcomes – RCT, direct comparison: upadacitinib + MTX vs. abatacept + MTX

Study	Outcomes															
	All-cause mortality	Clinical remission (CDAI ≤ 2.8; SDAI ≤ 3.3; Boolean definition)[a]	Low disease activity (CDAI ≤ 10; SDAI ≤ 11)[a, b]	Tender joints[c]	Swollen joints[c]	Pain (VAS)	Patient assessment of disease activity (VAS)	Physical functioning (HAQ-DI)	Fatigue (FACIT-Fatigue)	Morning stiffness (severity [NRS], duration)	Health status (EQ-5D VAS)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Infections[d]	Serious infections[d]
SELECT-CHOICE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. The derivation of the added benefit is primarily based on the CDAI, see Section 2.7.4.3.2 of the full dossier assessment.
b. Supplementary presentation: DAS28 (CRP) ≤ 3.2 and DAS28 (ESR) ≤ 3.2, see Appendix B.2 of the full dossier assessment.
c. Based on 28 joints.
d. All AEs of the MedDRA SOC "infections and infestations" are used for the recording of infections, and all SAEs for the recording of serious infections.

AE: adverse event; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; EQ-5D: European Quality of Life-5 Dimensions; ESR: erythrocyte sedimentation rate; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; MedDRA: Medical Dictionary for Regulatory Activities; MTX: methotrexate; NRS: numeric rating scale; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey; SDAI: Simplified Disease Activity Index; VAS: visual analogue scale; vs.: versus

2.5.2.2 Risk of bias

Table 25 describes the risk of bias for the results of the relevant outcomes.

Table 25: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: upadacitinib + MTX vs. abatacept + MTX

Study		Outcomes																		
			Clinical remission[a]			Low disease activity[a, b]														
	Study level	All-cause mortality	CDAI ≤ 2.8	SDAI ≤ 3.3	Boolean definition	CDAI ≤ 10	SDAI ≤ 11	Tender joints[c]	Swollen joints[c]	Pain (VAS)	Patient assessment of disease activity (VAS)	Physical functioning (HAQ-DI)	Fatigue (FACIT-Fatigue)	Morning stiffness (severity [NRS], duration)	Health status (EQ-5D VAS)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Infections[d]	Serious infections[d]
SELECT-CHOICE	L	H[e]	H[f]	H[f]	L	H[f]	H[f]	L	L	L	L	L	L	L	L	L	H[e]	H[e]	H[e]	H[e]

a. The derivation of the added benefit is primarily based on the CDAI, see Section 2.7.4.3.2 of the full dossier assessment.
b. Supplementary presentation: DAS28 (CRP) ≤ 3.2 and DAS28 (ESR) ≤ 3.2, see Appendix B.2 of the full dossier assessment.
c. Based on 28 joints.
d. All AEs of the MedDRA SOC "infections and infestations" are used for the recording of infections, and all SAEs for the recording of serious infections.
e. No information on patients with possibly incomplete observation; potential differences in follow-up observation periods between the treatment arms (upadacitinib arm: 30 days; abatacept arm: 70 days).
f. Large proportions of patients who were rated as non-responders due to missing values (> 10% in each of both study arms).

AE: adverse event; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; EQ-5D: European Quality of Life-5 Dimensions; ESR: erythrocyte sedimentation rate; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; H: high; HAQ-DI: Health Assessment Questionnaire-Disability Index; L: low; MedDRA: Medical Dictionary for Regulatory Activities; MTX: methotrexate; NRS: numeric rating scale; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey; SDAI: Simplified Disease Activity Index; VAS: visual analogue scale; vs.: versus

Deviating from the company, the risk of bias for the results on the outcome "all-cause mortality" and all side effect outcomes was rated as high, as there was no information on patients with possibly incomplete observation. Besides, there was an additional uncertainty for the results on these outcomes resulting from the potential differences in follow-up observation periods between the study arms.

Deviating from the company, the risk of bias of the results on the outcomes "clinical remission" and "low disease activity", when recorded using SDAI ≤ 3.3 and CDAI ≤ 2.8 or CDAI ≤ 10 and SDAI ≤ 11, was rated as high, as a large proportion of patients (> 10%) in each of both study arms were rated as non-responders due to missing values. In case of statistically significant results, however, in addition to the primary analysis in which patients with missing values were included as non-responders (see Section 2.5.1.2), sensitivity analyses were used in which missing values were imputed using alternative strategies. If the results were consistent, the certainty of conclusions of the results was not downgraded despite the high risk of bias.

Concurring with the company, the risk of bias for the results on the outcome "clinical remission", when recorded using the Boolean definition, was rated as low.

Concurring with the company, the risk of bias for the results on further outcomes of the categories of morbidity and health-related quality of life was rated as low.

Detailed reasons for the assessment of the risk of bias can be found in Section 2.7.4.2 of the full dossier assessment.

2.5.2.3 Results

Table 26 and Table 27 summarize the results of the comparison of upadacitinib + MTX with abatacept + MTX in adult patients with inadequate response or intolerance to pretreatment with one or more bDMARDs and/or tsDMARDs. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Tables on common AEs and discontinuation due to AEs are presented in Appendix A.2 of the full dossier assessment. Since, regarding the occurrence of SAEs, no events with a frequency of > 10 patients in one study arm occurred in the SELECT-CHOICE study, the frequencies of SAEs are not presented. Furthermore, the results on DAS28 (CRP) ≤ 3.2 and DAS28 (ESR) ≤ 3.2 are presented as additional information in Appendix B.2 of the full dossier assessment.

Table 26: Results (mortality, morbidity, health-related quality of life and side effects, dichotomous) – RCT, direct comparison: upadacitinib + MTX vs. abatacept + MTX

Study Outcome category Outcome	Upadacitinib + MTX		Abatacept + MTX		Upadacitinib + MTX vs. abatacept + MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
SELECT-CHOICE					
Mortality					
All-cause mortality	223	1 (0.4)	215	0 (0)	2.89 [0.12; 70.63]; 0.515[a]
Morbidity					
Clinical remission[b]					
CDAI ≤ 2.8	223	51 (22.9)	215	34 (15.8)	1.44 [0.97; 2.13]; 0.068[c, d]
SDAI ≤ 3.3	223	52 (23.3)	215	31 (14.4)	1.62 [1.08; 2.42]; 0.020[c, d]
Boolean definition	223	38 (17.0)	215	25 (11.6)	1.46 [0.92; 2.34]; 0.111[c, d]
Low disease activity[b]					
CDAI ≤ 10	223	137 (61.4)	215	115 (53.5)	1.15 [0.98; 1.36]; 0.081[c, d]
SDAI ≤ 11	223	140 (62.8)	215	115 (53.5)	1.18 [1.00; 1.38]; 0.045[c, d]
Physical functioning (HAQ-DI)[e]	223	171 (76.7)	215	149 (69.3)	1.11 [0.99; 1.24]; 0.086[c, d]
Fatigue (FACIT-Fatigue)[f]	223	160 (71.7)	215	141 (65.6)	1.10 [0.97; 1.25]; 0.147[c, d]
Health-related quality of life					
SF-36v2[g]					
Physical Component Summary	223	151 (67.7)	215	138 (64.2)	1.05 [0.92; 1.21]; 0.435[c, d]
Mental Component Summary	223	107 (48.0)	215	104 (48.4)	0.99 [0.82; 1.21]; 0.938[c, d]
Side effects					
AEs (supplementary information)	223	148 (66.4)	215	122 (56.7)	–
SAEs	223	5 (2.2)	215	1 (0.5)	4.82 [0.57; 40.93]; 0.149[a]
Discontinuation due to AEs	223	9 (4.0)	215	5 (2.3)	1.74 [0.59; 5.10]; 0.316[a]
Infections (SOC, AEs)	223	88 (39.5)	215	67 (31.2)	1.27 [0.98; 1.64]; 0.071[a]
Serious infections (SOC, SAEs)	223	2 (0.9)	215	0 (0)	4.82 [0.23; 99.85]; 0.309[a]

a. Effect estimation based on a generalized linear model with treatment as covariables.
b. The derivation of the added benefit is primarily based on the CDAI, see Section 2.7.4.3.2 of the full dossier assessment.
c. Effect estimation based on a generalized linear model with treatment and stratification variable prior bDMARD treatment (1 or 2 bDMARD therapies with the same mechanism of action vs. others) as covariables.
d. Imputation strategy NRI: Patients with missing values are rated as non-responders.
e. Patients with improvement by ≥ 0.22 points.
f. Patients with improvement by ≥ 4 points.
g. Patients with improvement by ≥ 5 points; only mean differences are available for the individual domains (physical functioning, physical role functioning, physical pain, general health perception, vitality, social functioning, emotional role functioning, mental wellbeing) (see Section 2.7.4.3.2 of the full dossier assessment).

AE: adverse event; bDMARD: biologic DMARD; CDAI: Clinical Disease Activity Index; CI: confidence interval; DMARD: disease-modifying antirheumatic drug; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; MTX: methotrexate; n: number of patients with (at least one) event; N: number of analysed patients; 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 27: Results (morbidity, continuous) – RCT, direct comparison: upadacitinib + MTX vs. abatacept + MTX

Study Outcome category Outcome	Upadacitinib + MTX			Abatacept + MTX			Upadacitinib + MTX vs. abatacept + MTX
	N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)[b]	MD [95% CI]; p-value[b]
SELECT-CHOICE							
Morbidity							
Tender joints[c]	221	14.5 (6.3)	−11.7 (0.4)	212	15.7 (6.7)	−11.2 (0.4)	−0.45 [−1.29; 0.40]; 0.299[d]
Swollen joints[c]	221	10.4 (4.7)	−8.5 (0.3)	212	11.4 (5.1)	−8.6 (0.3)	0.09 [−0.53; 0.71]; 0.780[d]
Pain (VAS)[e]	221	68.4 (20.2)	−40.3 (1.9)	212	71.1 (18.4)	−36.0 (1.9)	−4.31 [−8.75; 0.13]; 0.057[f]
Patient assessment of disease activity (VAS)[e]	223	66.7 (19.9)	−37.8 (1.9)	215	69.7 (20.0)	−35.6 (1.9)	−2.24 [−6.71; 2.22]; 0.321[f]
Morning stiffness[e]							
Severity (NRS)	223	6.4 (2.3)	−3.9 (0.2)	215	6.4 (2.3)	−3.4 (0.2)	−0.56 [−0.98; −0.13]; 0.010[f] Hedges' g: −0.25 [−0.43; −0.06]
Duration (min)	223	170.3 (242.3)	−94.2 (19.9)	215	209.7 (318.5)	−58.2 (21.1)	−36.09 [−83.86; 11.69]; 0.136[f]
Health status (EQ-5D VAS)[g]	223	43.7 (22.1)	29.5 (1.5)	215	45.1 (22.8)	25.4 (1.6)	4.10 [0.43; 7.77]; 0.027[f] Hedges' g: 0.21 [0.02; 0.40]

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b. Effect estimation based on an analysis of covariance with treatment and stratification variable prior bDMARD treatment (1 or 2 bDMARD therapies with the same mechanism of action; others) as fixed effects and baseline value as covariable.
c. Based on 28 joints.
d. Imputation of missing values using LOCF.
e. A negative change from baseline to end of study indicates improvement; a negative effect estimation indicates an advantage for upadacitinib + MTX.
f. Imputation of missing values using MI.
g. A positive change from baseline to end of study indicates improvement; a positive effect estimation indicates an advantage for upadacitinib + MTX.

bDMARD: biologic DMARD; CI: confidence interval; DMARD: disease-modifying antirheumatic drug; EQ-5D: European Quality of Life-5 Dimensions; LOCF: last observation carried forward; MD: mean difference; MI: multiple imputation; min: minutes; MTX: methotrexate; N: number of analysed patients; NRS: numeric rating scale; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Due to the high risk of bias, at most hints, e.g. of an added benefit or of greater or lesser harm, can be determined for the outcome "all-cause mortality" and all side effect outcomes on the basis of the SELECT-CHOICE study. For the outcomes "clinical remission" and "low disease activity", at most hints of an added benefit can be determined based on the CDAI due to the high risk of bias; the outcome-specific certainty of conclusions of the results may not be downgraded, however, so that at most indications can be derived (see Section 2.5.2.2). Due to the low risk of bias, at most indications of an added benefit can be determined for all other outcomes.

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 upadacitinib + MTX in comparison with abatacept + MTX; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Clinical remission

The outcome "clinical remission" was operationalized using the CDAI ≤ 2.8, the SDAI ≤ 3.3, or the Boolean definition according to ACR/EULAR. The assessment of clinical remission was primarily based on the CDAI ≤ 2.8.

For the outcome "clinical remission", no statistically significant difference between the treatment groups was shown on the basis of the CDAI ≤ 2.8. This was also shown in the Boolean definition. A statistically significant difference in favour of upadacitinib + MTX was shown for clinical remission operationalized using the SDAI ≤ 3.3.

However, there was an effect modification by the characteristic "age" for the primarily used CDAI ≤ 2.8. This resulted in an indication of an added benefit of upadacitinib + MTX versus abatacept + MTX for patients aged ≥ 65 years. For patients aged < 40 years and patients aged ≥ 40 years to < 65 years, however, there was no hint of an added benefit of upadacitinib + MTX versus abatacept + MTX; an added benefit is therefore not proven (see Section 2.5.2.4).

This deviates from the company's approach insofar as the company also derived an indication of an added benefit, but used the total relevant subpopulation of the SELECT-CHOICE study for its assessment on the basis of the CDAI ≤ 2.8. Besides, the company also considered the results of the total population of the study and the results for the part of the study population that does not concur with the relevant subpopulation. In addition, its assessment was based on the overall consideration of the results on CDAI ≤ 2.8, SDAI ≤ 3.3 and Boolean definition.

Low disease activity

The outcome "low disease activity" was operationalized as reaching the criteria of CDAI ≤ 10 and SDAI ≤ 11. The assessment of low disease activity was primarily based on the CDAI ≤ 10.

No statistically significant difference between the treatment groups was shown for the outcome "low disease activity" on the basis of the CDAI ≤ 10. On the basis of the SDAI ≤ 11, there was a statistically significant difference in favour of upadacitinib + MTX.

For the CDAI ≤ 10, however, there was an effect modification by the characteristic "disease activity at baseline", defined with the threshold value of the DAS28 (CRP) for high disease activity. This resulted in an indication of an added benefit of upadacitinib + MTX versus abatacept + MTX for patients with high disease activity at baseline (DAS28 [CRP] > 5.1). For patients without high disease activity at baseline (DAS28 [CRP] ≤ 5.1), however, there was no hint of an added benefit of upadacitinib + MTX versus abatacept + MTX; an added benefit is therefore not proven (see Section 2.5.2.4).

This deviates from the approach of the company, which used the total relevant subpopulation of the SELECT-CHOICE study for its assessment and, besides, did not primarily use the CDAI ≤ 10 for its assessment, but considered the results on CDAI ≤ 10, SDAI ≤ 11, as well as DAS28 (CRP) ≤ 3.2 and DAS28 (ESR) ≤ 3.2 in the overall consideration. On the basis of these results, the company derived an indication of an added benefit for the outcome "low disease activity" for the total relevant subpopulation.

Tender joints

For the outcome "tender joints", no statistically significant difference between the treatment groups was shown based on the mean differences. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with abatacept + MTX; an added benefit is therefore not proven.

This deviates from the approach of the company, which considered the tender and swollen joint count together and derived an indication of an added benefit on the basis of the response criterion of a maximum of 1 tender (or swollen) joint.

Swollen joints

For the outcome "swollen joints", no statistically significant difference between the treatment groups was shown based on the mean differences. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with abatacept + MTX; an added benefit is therefore not proven.

This deviates from the approach of the company, which considered the tender and swollen joint count together and derived an indication of an added benefit on the basis of the response criterion of a maximum of 1 swollen (or tender) joint.

Pain (VAS)

For the outcome "pain (VAS)", no statistically significant difference between the treatment groups was shown based on the mean differences. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with abatacept + MTX; an added benefit is therefore not proven.

This concurs with the assessment of the company, which based its assessment on the analyses on a response criterion, however.

Patient assessment of disease activity (VAS)

There was no statistically significant difference between the treatment groups for the outcome "patient assessment of disease activity (VAS)". This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with abatacept + MTX; an added benefit is therefore not proven.

This concurs with the company's assessment.

Physical functioning (HAQ-DI)

No statistically significant difference between the treatment groups was shown for the outcome "physical functioning (HAQ-DI). This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with abatacept + MTX; an added benefit is therefore not proven.

This concurs with the company's assessment.

Fatigue (FACIT-Fatigue)

For the outcome "fatigue (FACIT-Fatigue)", there was no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with abatacept + MTX; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morning stiffness (severity [NRS], duration)

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome "severity (NRS) of morning stiffness". The SMD in the form of Hedges' g was considered to check the relevance of the result. However, the 95% CI was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect was relevant. There was no statistically significant difference between the treatment groups for the duration of morning stiffness. This did not result in a hint of an added benefit of upadacitinib + MTX in comparison with abatacept + MTX for the severity (NRS) or for the duration of morning stiffness; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health status (EQ-5D VAS)

A statistically significant difference in favour of upadacitinib + MTX was shown for the outcome "health status (EQ-5D VAS)". The SMD in the form of Hedges' g was considered to check the relevance of the result. However, the 95% CI was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect was relevant. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with abatacept + MTX; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an indication of an added benefit.

Health-related quality of life

SF-36v2 – Physical and Mental Component Summary

No statistically significant difference between the treatment groups was shown for the Physical Component Summary or for the Mental Component Summary of the SF-36v2. This resulted in no hint of an added benefit of upadacitinib + MTX in comparison with abatacept + MTX for the outcome "health-related quality of life (SF-36v2)"; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

SAEs, discontinuation due to AEs

No statistically significant differences were shown between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". In each case, this resulted in no hint of greater or lesser harm from upadacitinib + MTX in comparison with abatacept + MTX; greater or lesser harm is therefore not proven for each of these outcomes.

This concurs with the company's assessment.

Infections

No statistically significant difference between the treatment groups was shown for the outcome "infections". This resulted in no hint of greater or lesser harm from upadacitinib + MTX in comparison with abatacept + MTX; greater or lesser harm is therefore not proven.

Besides the results for the total relevant subpopulation of the SELECT-CHOICE study, the company also considered the results of the total population of the study and the results for the part of the study population that does not concur with the relevant subpopulation, and arrived at the same assessment based on this consideration.

Serious infections

No statistically significant difference between the treatment groups was shown for the outcome "serious infections". This resulted in no hint of greater or lesser harm from upadacitinib + MTX in comparison with abatacept + MTX; greater or lesser harm is therefore not proven.

This deviates from the approach of the company, which did not consider the outcome „serious infections" in its assessment.

2.5.2.4 Subgroups and other effect modifiers

For adult patients with inadequate response or intolerance to pretreatment with one or more bDMARDs and/or tsDMARDs, the following predefined subgroup characteristics were used for the present assessment:

- age (< 40 years, 40 to < 65 years, ≥ 65 years)
- sex (female, male)
- geographical region (North America, South/Central America, Eastern Europe, Western Europe, other)
- disease activity at baseline based on the DAS28 (CRP) (DAS28 [CRP] ≤ 5.1 [no high disease activity], DAS28 [CRP] > 5.1 [high disease activity]
- pretreatment with bDMARD (failure to 1 or 2 bDMARDs with the same mechanism of action, failure to different mechanisms of action or ≥ 3 bDMARDs with the same mechanism of action)

Apart from the subgroup characteristic "pretreatment with bDMARD", the company presented subgroup analyses for all characteristics relevant for the present benefit assessment. Apart from the outcomes "serious infections", "tender joints" and "swollen joints", the company presented subgroup analyses for the other characteristics for all outcomes relevant for the present benefit assessment. The company did not consider the outcome "serious infections" in its assessment, and, for the outcomes "tender joints" and "swollen joints", the company only presented subgroup analyses on the basis of the response criterion of at most 1 tender or swollen joint. These analyses were not used for the present benefit assessment (see Section 2.7.4.3.2 of the full dossier assessment for reasons).

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there must be 10 events in at least one subgroup.

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

Table 28 summarizes the subgroup results of the comparison of upadacitinib + MTX with abatacept + MTX in adult patients with inadequate response or intolerance to pretreatment with one or more bDMARDs and/or tsDMARDs.

Table 28: Subgroup results (morbidity, dichotomous) – RCT, direct comparison: upadacitinib + MTX vs. abatacept + MTX

Study Outcome Characteristic Subgroup	Upadacitinib + MTX		Abatacept + MTX		Upadacitinib + MTX vs. abatacept + MTX	
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
SELECT-CHOICE						
Clinical remission						
CDAI ≤ 2.8[a]						
Age						
< 40 years	18	1 (5.6)	21	3 (14.3)	0.39 [0.04; 3.42][b]	0.394
≥ 40 – < 65 years	156	37 (23.7)	140	28 (20.0)	1.19 [0.77; 1.83][b]	0.442
≥ 65 years	49	13 (26.5)	54	3 (5.6)	4.78 [1.45; 15.77][b]	0.010
Total					Interaction:	0.024[c]
SDAI ≤ 3.3[a]						
Age						
< 40 years	18	1 (5.6)	21	3 (14.3)	0.39 [0.04; 3.42][b]	0.394
≥ 40 – < 65 years	156	36 (23.1)	140	26 (18.6)	1.24 [0.79; 1.95][b]	0.344
≥ 65 years	49	15 (30.6)	54	2 (3.7)	8.27 [1.99; 34.33][b]	0.004
Total					Interaction:	0.004[c]
Low disease activity						
CDAI ≤ 10[a]						
DAS28 (CRP), (disease activity at baseline)						
≤ 5.1	59	40 (67.8)	46	38 (82.6)	0.82 [0.66; 1.02][b]	0.079
> 5.1	164	97 (59.1)	168	77 (45.8)	1.29 [1.05; 1.59][b]	0.016
Total					Interaction:	0.004[c]
SDAI ≤ 11[a]						
DAS28 (CRP), (disease activity at baseline)						
≤ 5.1	59	42 (71.2)	46	37 (80.4)	0.89 [0.71; 1.10][b]	0.268
> 5.1	164	98 (59.8)	168	77 (45.8)	1.30 [1.06; 1.60][b]	0.012
Total					Interaction:	0.012[c]

a. Imputation strategy NRI: Patients with missing values are rated as non-responders.
b. Effect estimation based on a generalized linear model with treatment and stratification variable prior bDMARD treatment (1 or 2 bDMARD therapies with the same mechanism of action vs. others) as covariables.
c. p-value for the interaction term of generalized linear model with treatment, subgroup and treatment x subgroup as covariables.

bDMARD: biologic DMARD; CDAI: Clinical Disease Activity Index; CI: confidence interval; CRP: C-reactive protein; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; n: number of patients with event; N: number of analysed patients; NRI: non-responder imputation; RCT: randomized controlled trial; RR: relative risk; SDAI: Simplified Disease Activity Index; vs.: versus

There were effect modifications for the outcomes “clinical remission” and “low disease activity”, each operationalized using the CDAI and SDAI. For both operationalizations, statistically significant differences between the treatment groups were shown for the same subgroups. For both outcomes, the results of the CDAI were primarily used for the assessment of the added benefit for the present benefit assessment.

Due to large proportions of patients rated as non-responders due to missing values in the analyses based on the CDAI for both outcomes (> 10% in both study arms), the results on these outcomes had a high risk of bias. The Institute conducted its own calculations using alternative imputation strategies to check whether the certainty of conclusions of the results had to be downgraded due to the high risk of bias (see Section 2.5.2.2).

Table 29 summarizes the results of the sensitivity analyses from the Institute’s calculation for the outcomes “clinical remission” and “low disease activity”, each for the primarily used operationalization using the CDAI, for subgroups with statistically significant difference between the treatment groups. Since the results of the CDAI were primarily used for the present benefit assessment, no sensitivity analyses on the SDAI were conducted.

Table 29: Sensitivity analyses (morbidity, dichotomous) – RCT, direct comparison: upadacitinib + MTX vs. abatacept + MTX

Study Outcome Subgroup Imputation strategy	Upadacitinib + MTX N	 Patients with event n (%)	Abatacept + MTX N	 Patients with event n (%)	Upadacitinib + MTX vs. abatacept + MTX RR [95% CI]	 p-value
SELECT-CHOICE						
Clinical remission						
CDAI ≤ 2.8						
Age ≥ 65 years						
NRI[a]	49	13 (26.5)	54	3 (5.6)	4.78 [1.45; 15.77][b]	0.010[b]
Sensitivity analyses:						
NRI with variance correction[a]	49	13 (26.5)	54	3 (5.6)	4.78 [1.37; 16.69][c, d]	0.014[d]
ACA[e]	41	13 (31.7)	50	3 (6.0)	5.28 [1.61; 17.29][c]	0.006[c]
ICA-pc[f]	49	– (27.51)	54	– (6.0)	4.59 [1.37; 15.29][c, d]	0.013[d]
Low disease activity						
CDAI ≤ 10						
DAS28 (CRP) > 5.1, (high disease activity at baseline)						
NRI[a]	164	97 (59.1)	168	77 (45.8)	1.29 [1.05; 1.59][b]	0.016[b]
Sensitivity analyses:						
NRI with variance correction[a]	164	97 (59.1)	168	77 (45.8)	1.29 [1.03; 1.61][c, d]	0.024[d]
ACA[e]	145	97 (66.9)	147	77 (52.4)	1.28 [1.05; 1.55][c]	0.013[c]
ICA-pc[f]	164	– (65.2)	147	– (52.4)	1.25 [1.02; 1.51][c, d]	0.027[d]

a. In both treatment groups, patients with missing values are rated as non-responders.
b. Primary analysis: effect estimation based on a generalized linear model with treatment and stratification variable prior bDMARD treatment (1 or 2 bDMARD therapies with the same mechanism of action vs. others) as covariables.
c. Institute's calculation, asymptotic.
d. Institute's calculation, estimation of variance according to the dataset re-sizing approach (approach W3 in [25]).
e. Analysis is exclusively based on patients with complete observation.
f. In both treatment groups, the missing values are imputed according to the observed risk in the control group.

ACA: available case analysis; bDMARD: biologic DMARD; CDAI: Clinical Disease Activity Index; CI: confidence interval; CRP: C-reactive protein; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; DMARD: disease-modifying antirheumatic drug; ICA-pc: imputed case analysis according to risk in the control group; MTX: methotrexate; n: number of patients with event; N: number of analysed patients; NRI: non-responder imputation; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Morbidity

Clinical remission

There was an effect modification by the characteristic "age" for the outcome "clinical remission". A statistically significant difference in favour of upadacitinib + MTX was shown for patients aged ≥ 65 years. The sensitivity analyses using alternative imputation strategies

confirmed this effect regarding statistical significance. This resulted in an indication of an added benefit of upadacitinib + MTX versus abatacept + MTX for patients aged ≥ 65 years. For patients aged < 40 years and patients aged ≥ 40 to < 65 years, there was no statistically significant difference between the treatment groups. For these patients, this resulted in no hint of an added benefit of upadacitinib + MTX in comparison with abatacept + MTX; an added benefit is therefore not proven in each case.

Low disease activity

There was an effect modification by the characteristic "disease activity at baseline", defined with the threshold value of the DAS28 (CRP) for high disease activity (DAS28 [CRP] > 5.1) for the outcome "low disease activity". A statistically significant difference in favour of upadacitinib + MTX was shown for patients with high disease activity at baseline. The sensitivity analyses using alternative imputation strategies confirmed this effect regarding statistical significance. This resulted in an indication of an added benefit of upadacitinib + MTX versus abatacept + MTX for patients with high disease activity at baseline (DAS28 [CRP] > 5.1). No statistically significant difference between the treatment groups was shown for patients without high disease activity at baseline (DAS28 [CRP] ≤ 5.1). For these patients, this resulted in no hint of an added benefit of upadacitinib + MTX in comparison with abatacept + MTX; an added benefit is therefore not proven.

2.5.3 Probability and extent of added benefit

Probability and extent of added benefit for adult patients with inadequate response or intolerance to pretreatment with one or more bDMARDs and/or tsDMARDs at outcome level is derived below, 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 the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.5.2 (see Table 30).

Determination of the outcome category for symptom outcomes

Clinical remission and low disease activity

Concurring with the company, the outcomes "clinical remission" and "low disease activity" are allocated to the outcome category of serious/severe symptoms/late complications, as it can be assumed on the basis of the information on disease activity at baseline that the majority of the patients of the relevant subpopulation had serious/severe symptoms at this time point (see Table 22).

Table 30: Extent of added benefit at outcome level: upadacitinib + MTX vs. abatacept + MTX (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Upadacitinib + MTX vs. abatacept + MTX** **Proportion of events (%) or mean change** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0.4% vs. 0% RR: 2.89 [0.12; 70.63]; p = 0.515	Lesser benefit/added benefit not proven
Morbidity		
Clinical remission (CDAI ≤ 2.8)		
Age		
< 40 years	5.6% vs. 14.3% RR: 0.39 [0.04; 3.42]; p = 0.394	Lesser benefit/added benefit not proven
≥ 40 – < 65 years	23.7% vs. 20.0% RR: 1.19 [0.77; 1.83]; p = 0.442	Lesser benefit/added benefit not proven
≥ 65 years	26.5% vs. 5.6% RR: 4.78 [1.45; 15.77]; p = 0.010 RR[c]: 0.21 [0.06; 0.69] probability: „indication"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "major"
Low disease activity (CDAI ≤ 10)		
DAS28 (CRP), (disease activity at baseline)		
≤ 5.1	67.8% vs. 82.6% RR: 0.82 [0.66; 1.02]; p = 0.079	Lesser benefit/added benefit not proven
> 5.1	59.1% vs. 45.8% RR: 1.29 [1.05; 1.59]; p = 0.016 RR[c]: 0.78 [0.63; 0.95] probability: „indication"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "minor"
Tender joints[d]	Mean change: −11.7 vs. −11.2 MD: −0.45 [−1.29; 0.40]; p = 0.299	Lesser benefit/added benefit not proven
Swollen joints[d]	Mean change: −8.5 vs. −8.6 MD: 0.09 [−0.53; 0.71]; p = 0.780	Lesser benefit/added benefit not proven
Pain (VAS)	Mean change: −40.3 vs. −36.0 MD: −4.31 [−8.75; 0.13]; p = 0.057	Lesser benefit/added benefit not proven
Patient assessment of disease activity (VAS)	Mean change: −37.8 vs. −35.6 MD: −2.24 [−6.71; 2.22]; p = 0.321	Lesser benefit/added benefit not proven
Physical functioning (HAQ-DI)[e]	76.7% vs. 69.3% RR: 1.11 [0.99; 1.24]; p = 0.086	Lesser benefit/added benefit not proven
Fatigue (FACIT-Fatigue)[f]	71.7% vs. 65.6% RR: 1.10 [0.97; 1.25]; p = 0.147	Lesser benefit/added benefit not proven

Table 30: Extent of added benefit at outcome level: upadacitinib + MTX vs. abatacept + MTX (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Upadacitinib + MTX vs. abatacept + MTX** **Proportion of events (%) or mean change** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Morning stiffness		
Severity (NRS)	Mean change: −3.9 vs. −3.4 MD: −0.56 [−0.98; −0.13]; p = 0.010 Hedges' g: −0.25 [−0.43; −0.06][g]	Lesser benefit/added benefit not proven
Duration (min)	Mean change: −94.2 vs. −58.2 MD: −36.09 [−83.86; 11.69]; p = 0.136	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	Mean change: 29.5 vs. 25.4 MD: 4.10 [0.43; 7.77]; p = 0.027 Hedges' g: 0.21 [0.02; 0.40][g]	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36v2[h]		
Physical Component Summary	67.7% vs. 64.2% RR: 1.05 [0.92; 1.21]; p = 0.435	Lesser benefit/added benefit not proven
Mental Component Summary	48.0% vs. 48.4% RR: 0.99 [0.82; 1.21]; p = 0.938	Lesser benefit/added benefit not proven
Side effects		
SAEs	2.2% vs. 0.5% RR: 4.82 [0.57; 40.93]; p = 0.149	Greater/lesser harm not proven
Discontinuation due to AEs	4.0% vs. 2.3% RR: 1.74 [0.59; 5.10]; p = 0.316	Greater/lesser harm not proven
Infections (SOC, AEs)	39.5% vs. 31.2% RR: 1.27 [0.98; 1.64]; p = 0.071	Greater/lesser harm not proven
Serious infections (SOC, SAEs)	0.9% vs. 0% RR: 4.82 [0.23; 99.85]; p = 0.309	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d. Based on 28 joints.
e. Patients with improvement by ≥ 0.22 points.
f. Patients with improvement by ≥ 4 points.
g. 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, the presence of a relevant effect cannot be inferred.
h. Patients with improvement by ≥ 5 points.

AE: adverse event; CDAI: Clinical Disease Activity Index; CI: confidence interval; CI_u: upper limit of confidence interval; CRP: C-reactive protein; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; EQ-5D: European Quality of Life-5 Dimensions; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; MD: mean difference; min: minute; MTX: methotrexate; NRS: numeric rating scale; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.5.3.2 Overall conclusion on added benefit

Table 31 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 31: Positive and negative effects from the assessment of upadacitinib + MTX in comparison with abatacept + MTX

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ Clinical remission (CDAI ≤ 2.8) ▫ age (≥ 65 years) indication of an added benefit – extent: „major" ▪ Low disease activity (CDAI ≤ 10) ▫ DAS28 (CRP) > 5.1, (high disease activity at baseline) indication of an added benefit – extent: "minor"	–
For research question 3, only data are available for the subpopulation of patients for whom a combination therapy with MTX is an option. No data are available for patients for whom monotherapy with upadacitinib is an option.	
CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; MTX: methotrexate	

In the overall consideration, there were exclusively positive effects of upadacitinib + MTX in comparison with abatacept + MTX for adult patients with inadequate response or intolerance to pretreatment with one or more bDMARDs and/or tsDMARDs. This concerns the outcomes "clinical remission" and "low disease activity", in each case for different subgroups. For both outcomes, the sensitivity analyses confirmed the primary analyses in the relevant subgroups, both regarding statistical significance and extent. The advantage of upadacitinib + MTX, resulting for the primary treatment goal of clinical remission, concerned the notably smaller subgroup of patients aged ≥ 65 years. The larger subgroup of patients with high disease activity at baseline, for whom there was an advantage of upadacitinib + MTX for the alternative treatment goal of low disease activity, in contrast, constituted the majority of the study population. In addition, it can be assumed on the basis of the information on the total population of the SELECT-CHOICE study that this subgroup also included patients of the age group of ≥ 65 years. However, information on the extent to which the two subgroups overlap is not available for the relevant subpopulation of the study. Thus, the subgroup of patients with high disease activity at baseline was used for the derivation of the added benefit.

Since the positive effects are not opposed by negative effects, there is overall an indication of a minor added benefit for patients with high disease activity at baseline (DAS28 [CRP] > 5.1).

In summary, there is an indication of a minor added benefit of upadacitinib + MTX versus abatacept + MTX for adult patients with moderate to severe active rheumatoid arthritis with high disease activity (DAS28 [CRP] > 5.1) and inadequate response or intolerance to pretreatment with one or more bDMARDs and/or tsDMARDs.

No data are available for patients for whom monotherapy with upadacitinib is an option. The added benefit is not proven for this patient group.

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit for adult patients with inadequate response or intolerance to pretreatment with one or more bDMARDs and/or tsDMARDs on the basis of the total relevant subpopulation, without differentiating between the patient groups for whom a combination therapy of upadacitinib + MTX or monotherapy with upadacitinib is an option.

2.6 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of upadacitinib in comparison with the ACT is summarized in Table 32.

Table 32: Upadacitinib – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
Adults with moderate to severe active rheumatoid arthritis			
1	Patients without poor prognostic factors[b] who have responded inadequately to, or who are intolerant to prior treatment with one csDMARD[c] (including MTX)	Alternative csDMARDs[c] if suitable (e.g. MTX, leflunomide) as monotherapy or combination therapy	Added benefit not proven
2	Patients for whom a first therapy with bDMARDs or tsDMARDs is indicated[d]	bDMARDs or tsDMARDs (abatacept or **adalimumab** or baricitinib or certolizumab pegol or etanercept or golimumab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability)	Combination with MTX: indication of considerable added benefit
			Monotherapy: added benefit not proven
3	Patients who have responded inadequately to, or who are intolerant to prior treatment with one or more bDMARDs and/or tsDMARDs	Switching of bDMARD or tsDMARD therapy (**abatacept** or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability; or, in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on prior therapy[e]	Combination with MTX: ▪ Patients with high disease activity (DAS28 [CRP] > 5.1): ▫ indication of minor added benefit ▪ Patients without high disease activity (DAS28 [CRP] ≤ 5.1): ▫ added benefit not proven
			Monotherapy: added benefit not proven

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. Poor prognostic factors: detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antigen 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. In the G-BA's specification of the ACT, csDMARDs are referred to as "classical DMARDs". The present benefit assessment uses the term "csDMARDs".
d. This comprises both patients with poor prognostic factors who have responded inadequately to, or who have not tolerated previous treatment with one csDMARD (including MTX), and patients who have responded inadequately to or have not tolerated previous treatment with several csDMARDs (including MTX).
e. Switching the mode of action should be considered depending on the prior therapy.

ACT: appropriate comparator therapy; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; CRP: C-reactive protein; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate; tsDMARD: targeted synthetic DMARD

The approach for deriving an overall conclusion on the 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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