IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Tofacitinib (rheumatoid arthritis) –

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

Extract

[1] Translation of Sections 2.1 to 2.8 of the dossier assessment *Tofacitinib (Rheumatoide Arthritis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 July 2017). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BID	twice daily
CDAI	Clinical Disease Activity Index
cDMARD	conventional disease-modifying antirheumatic drug
CTCAE	Common Terminology Criteria for Adverse Events
DAS28	Disease Activity Score-28
DMARD	disease-modifying antirheumatic drug
ESR	erythrocyte sedimentation rate
FACIT-Fatigue	Fatigue, measured using the Functional Assessment of Chronic Illness Therapy
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)
MOS	Medical Outcome Study
MTX	Methotrexate
RCT	randomized controlled trial
SAE	serious adverse event
SF-36v2	Short Form (36) version 2 Health Survey
SF-36v2 acute	Short Form (36) version 2 Health Survey acute
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	Visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug tofacitinib. 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 27 April 2017.

Research question

The aim of this report was to assess the added benefit of tofacitinib in combination with methotrexate (MTX) in comparison with the appropriate comparator therapy (ACT) in adult patients with moderate to severe active rheumatoid arthritis with inadequate response to one or several disease-modifying antirheumatic drugs (DMARDs) or intolerance to such treatments. Tofacitinib may be used as monotherapy when MTX is not tolerated or treatment with MTX is unsuitable.

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

Table 2: Research questions on the benefit assessment of tofacitinib

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

a: Research questions 1, 2, 3 and 4 correspond to the respective subpopulations b, c, d and e of the company.
b: 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**.
c: Poor prognostic factors, for instance, detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.
d: In the report referred to as cDMARD.
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; cDMARD: conventional disease-modifying antirheumatic drug; DAS: Disease Activity Score; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate

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

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

Results

The study pool for the benefit assessment of tofacitinib in comparison with the ACT consisted of the RCT ORAL STANDARD and corresponded to the study pool of the company. The study compared tofacitinib + MTX with adalimumab + MTX. Due to its design and the patients included, the ORAL STANDARD study was suitable for the derivation of conclusions on the added benefit of tofacitinib for research questions 2 and 3 on the basis of subpopulations.

In addition to the included ORAL STANDARD study, results of the potentially relevant ORAL STRATEGY study on the comparison of tofacitinib + MTX versus tofacitinib monotherapy versus adalimumab + MTX in patients with moderate to severe active rheumatoid arthritis were published on 16 June 2017. The company provided no data of this study in its dossier. It justified this by claiming that no results were available. Therefore, the ORAL STRATEGY study was no component of the study pool for the present assessment. It cannot be conclusively assessed whether the company would have been able to present results of the ORAL STRATEGY study for the benefit assessment. Irrespective of this, the present assessment was not based on the total data available at this time point.

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

Research questions 2 and 3

Study characteristics

The ORAL STANDARD study was a randomized, multicentre, double-blind, parallel-group phase 3 study. The study included adult patients with active rheumatoid arthritis and inadequate response to MTX. The study comprised a total of five study arms. For the present assessment, only the study arms tofacitinib 5 mg bid + MTX were relevant for comparison with adalimumab + MTX. Treatment with tofacitinib and adalimumab was in compliance with the approval. The planned treatment period was 12 months.

Relevant subpopulations for research questions 2 and 3

The subpopulation of patients with poor prognostic factors and inadequate response to prior treatment with 1 cDMARD was relevant for research question 2. This relevant subpopulation of the ORAL STANDARD study comprised 81 patients in the intervention arm and 76 patients in the comparator arm with poor prognostic factors who showed inadequate responses to the cDMARD MTX.

The subpopulation of patients in the ORAL STANDARD study with inadequate response to prior treatment with several cDMARDs was relevant for research question 3. This relevant subpopulation comprised 102 patients in the intervention arm and 104 patients in the comparator arm.

Risk of bias

The risk of bias at study level was rated as low. At outcome level, the risk of bias for research questions 2 and 3 for the outcome “discontinuation due to AEs” was rated as low. The risk of bias was rated as high for all further outcomes for which analyses were available for the relevant subpopulations.

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

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

Mortality

- All-cause mortality

There were no usable data for the outcome "all-cause mortality" for the subpopulation. Only 1 patient of the total study population died during the observation period in the relevant study arms, namely in the adalimumab arm. This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

Morbidity

- remission
- low disease activity
- tender joints
- swollen joints
- pain, measured using a visual analogue scale (VAS)
- disease activity, measured using a VAS
- fatigue, measured using the Functional Assessment of Chronic Illness Therapy ([FACIT]-Fatigue)
- physical functioning, measured using the Health Assessment Questionnaire-Disability Index (HAQ-DI)
- Sleep disturbances, measured using the MOS sleep scale

Health-related quality of life

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

No statistically relevant difference between the treatment groups was shown for the endpoints "remission" (CDAI ≤ 2.8), "low disease activity" (DAS28-4 ESR ≤ 3.2), "physical functioning" (improvement in HAQ-DI by ≥ 0.22 points), "tender joints", "swollen joints", "sleep disturbances", "pain", "disease activity", "fatigue" (FACIT-Fatigue) as well as for the physical and mental component summary of the SF-36v2 acute. This resulted in no hint of an

added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for these outcomes; an added benefit is therefore not proven.

Side effects

- Serious adverse events (SAE)

A statistically significant difference to the disadvantage of tofacitinib + MTX was shown for the outcome "SAEs". Moreover, there was an effect modification by the characteristic "age" for this outcome. For patients ≤ 65 years, this resulted in a hint of greater harm of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome. For patients > 65 years, this resulted in no hint of greater or lesser harm from tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; greater or lesser harm is therefore not proven for patients > 65 years.

- Discontinuation due to AEs
- Infections

No statistically significant difference between the treatment groups was shown for the outcomes "discontinuation due to AEs" and "infections (AEs of the System Organ Class [SOC] "infections and infestations"). Hence, for these outcomes, there was no hint of greater or lesser harm from tofacitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven.

- Serious Infections

There were no usable data on the outcome "serious infections" for the relevant subpopulation, because the company had not analysed this prespecified outcome for the subpopulations. Given the missing data for this outcome, there was altogether no hint of greater or lesser harm from tofacitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[4]

Patients ≤ 65 years

Overall, only a negative effect was found for patients ≤ 65 years. There was one hint of greater harm with the extent "major" in the category "serious/severe side effects (SAEs)".

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

Hence, there is a hint of lesser benefit of tofacitinib in comparison with adalimumab for patients ≤ 65 with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with 1 cDMARD and with poor prognostic factors.

Patients > 65 years

In summary, there are neither positive nor negative effects for patients > 65 years. This resulted in no hint of an added benefit of tofacitinib in comparison with the ACT for patients > 65 years with moderate to severe active rheumatoid arthritis who have responded inadequately to prior treatment with 1 cDMARDs and with poor prognostic factors. An added benefit is therefore not proven.

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

Mortality

- All-cause mortality

There were no usable data for the outcome "all-cause mortality" for the subpopulation. Only one patient died during the observation period in the relevant study arms, namely in the adalimumab arm. This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

Morbidity

- remission
- low disease activity
- tender joints
- swollen joints
- pain, measured using a VAS
- disease activity, measured using a VAS
- fatigue, measured using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
- physical functioning, measured using the HAQ-DI
- Sleep disturbances, measured using the MOS sleep scale

Health-related quality of life

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

Nor was a statistically relevant difference between the treatment groups observed for the endpoints "remission" (CDAI ≤ 2.8), "low disease activity" (DAS28-4 ESR ≤ 3.2), "physical

functioning" (improvement in HAQ-DI by ≥ 0.22 points), "tender joints", "swollen joints", "sleep disturbances", "pain", "disease activity", "fatigue" (FACIT-Fatigue) or for the physical and mental component summary of the SF-36v2 acute. This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for these outcomes; an added benefit is therefore not proven.

Side effects

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

No statistically significant difference between the treatment groups was shown for the outcomes "SAEs", "discontinuation due to AEs" and "infections". The company presented no analyses for the relevant subpopulation for the outcome "serious infections". Hence, for these outcomes, there was no hint of greater or lesser harm from tofacitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven.

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

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

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

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

Table 3: Tofacitinib – probability and extent of added benefit

Research question[a]	**Therapeutic indication**	**ACT**[b]	**Probability and extent of added benefit**
1	Patients without poor prognostic factors[c] who have responded inadequately to prior treatment with 1 conventional DMARD	Alternative conventional DMARDs (e.g. MTX, leflunomide), if suitable, as monotherapy or combination therapy	Added benefit not proven
2	Patients with poor prognostic factors[c] who have responded inadequately to prior treatment with 1 conventional DMARD[d].	Biologic disease-modifying antirheumatic drug (bDMARD) in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance	*Patients ≤ 65 years* Hint of lesser benefit *Patients > 65 years* Added benefit not proven
3	Patients who have responded inadequately to prior treatment with several DMARDs (conventional DMARDs, including MTX)	Biologic disease-modifying antirheumatic drug (bDMARD) in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance	Added benefit not proven
4	Patients who have responded inadequately to prior treatment with 1 or several bDMARDs	Switching of bDMARD treatment (adalimumab or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab); in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance; or in patients with severe rheumatoid arthritis, rituximab under consideration of the approval depending on prior therapy	Added benefit not proven

a: Research questions 1, 2, 3 and 4 correspond to the respective subpopulations b, c, d and e of the company.
b: 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**.
c: Poor prognostic factors, for instance, detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.
d: According to the SPC, tofacitinib is also approved for patients who have not tolerated prior treatment with a DMARD [3]. The relevant subpopulation of the included study for the assessment of the added benefit (only patients who have shown inadequate response to MTX) therefore does not completely cover the therapeutic indication. It remains unclear whether the observed effects can be transferred to patients who have not tolerated prior treatment with a DMARD.

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

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 this report was to assess the added benefit of tofacitinib in combination with MTX in comparison with the ACT in adult patients with moderate to severe active rheumatoid arthritis with inadequate response to one or several DMARDs or intolerance to such treatments. Tofacitinib may be used as monotherapy when MTX is not tolerated or treatment with MTX is unsuitable.

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

Table 4: Research questions on the benefit assessment of tofacitinib

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

a: Research questions 1, 2, 3 and 4 correspond to the respective subpopulations b, c, d and e of the company.
b: 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**.
c: Poor prognostic factors, for instance, detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.
d: in the report referred to as cDMARD.

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

The company principally followed the ACT specified by the G-BA. However, it additionally subdivided the comparator therapy for all research questions by patients who tolerated MTX and those who were MTX-intolerant. No subdivision was conducted in the present benefit assessment (see Section 2.9.1 of the full dossier assessment).

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on tofacitinib (status: 8 February 2017)
- bibliographical literature search on tofacitinib (last search on 2 February 2017)
- search in trial registries for studies on tofacitinib (last search on 2 February 2017)

To check the completeness of the study pool:

- search in trial registries for studies on tofacitinib (last search on 16 May 2017)

The check identified no additional relevant study.

2.3.1 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: tofacitinib + MTX versus adalimumab + MTX

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
A3921064 (ORAL STANDARD[b])	Yes	Yes	No

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

The study pool for the benefit assessment of tofacitinib in comparison with the ACT consisted of the RCT ORAL STANDARD and concurred with the study pool of the company. The study compared tofacitinib + MTX with adalimumab + MTX. Due to its design and the patients included, the ORAL STANDARD study was suitable for the derivation of

conclusions on the added benefit of tofacitinib for research questions 2 and 3 on the basis of subpopulations (see also Sections 2.5 and 2.6 of the full dossier assessment).

Concurring with the information provided by the company, no data were available for the benefit assessment of tofacitinib in comparison with the ACT for research questions 1 and 4.

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

Table 6: Tofacitinib - overview of the data available for the benefit assessment for each research question

Research question[a]	Population	Data presented
1	Patients without poor prognostic factors[b] who have responded inadequately to prior treatment with 1 conventional DMARD[c]	-
2	Patients with poor prognostic factors[b] who have responded inadequately to prior treatment with 1 conventional DMARD[c].	RCT (subpopulation[d] of the ORAL STANDARD study)
3	Patients who have responded inadequately to prior treatment with several DMARDs (conventional DMARDs, including MTX)	RCT (subpopulation[e] of the ORAL STANDARD study)
4	Patients who have responded inadequately to prior treatment with 1 or several bDMARDs	-

a: Research questions 1, 2, 3 and 4 correspond to the respective subpopulations b, c, d and e of the company.
b: Poor prognostic factors, for instance, detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.
c: In the report referred to as cDMARD.
d: Referred to as “subpopulation c” by the company.
e: Referred to as “subpopulation d” by the company.
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DAS: Disease Activity Score; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; RCT: randomized controlled trial

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

In addition to the included ORAL STANDARD study, results of the potentially relevant ORAL STRATEGY study on the comparison of tofacitinib + MTX versus tofacitinib monotherapy versus adalimumab + MTX in patients with moderate to severe active rheumatoid arthritis were published on 16 June 2017 [4]. The company provided no data of this study in its dossier. It justified this by claiming that no results were available (see Section 2.9.2.3.2 of the full dossier assessment). Therefore, the ORAL STRATEGY study was no component of the study pool for the present assessment. It cannot be conclusively assessed whether the company would have been able to present results of the ORAL STRATEGY

study for the benefit assessment. Irrespective of this, the present assessment was not based on the total data available at this time point.

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

2.4.1 Results on added benefit (research question 1)

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

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

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

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

2.4.3 List of included studies (research question 1)

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

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

2.5.1 Study characteristics (research question 2)

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study Duration	Location and period of study	Primary outcome; secondary outcomes[a]
ORAL STANDARD	RCT, double-blind, parallel	Adult patients with active rheumatoid arthritis and inadequate response under treatment with MTX continuous administration of MTX for ≥ 4 months and in stable doses of 7.5 mg to 25 mg per week ≥ 6 weeks before the first administration of the study medication no treatment failure under tumour necrosis factor inhibitor (TNFi) and no specific AEs following the intake of TNFi	Each in combination with MTX: tofacitinib 5 mg bid (N = 204) tofacitinib 10 mg bid (N = 201)[b] placebo → tofacitinib 5 mg bid (N = 56)[b] placebo → tofacitinib 10 mg bid (N = 52)[b] adalimumab 40 mg (N = 204) Relevant analysed subpopulation thereof[c]: tofacitinib 5 mg bid (N = 81) adalimumab 40 mg (N = 76)	Screening: 1 month Treatment: 12 months[d] Follow-up: 28 days after the last administration of the study medication (safety)	115 centres in Australia, Bosnia and Herzegovina, Bulgaria, Canada, Chile, Costa Rica, Croatia, Czech Republic, Denmark, Dominican Republic, Finland, Germany, Korea, Mexico, Philippines, Poland, Slovak Republic, Spain, Thailand, USA, United Kingdom 05/2009-03/2011	Primary: ACR20 at month 6 HAQ-DI at month 3 DAS28-4 ESR < 2.6 at month 6 Secondary: Morbidity health-related quality of life AEs

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.
b: The study arm is not relevant for the assessment and is not shown in the next tables.
c: Patients with poor prognostic factors who have responded inadequately to prior treatment with 1 cDMARD.
d: During the 6-month double-blind placebo-controlled study phase all patients from the two placebo arms with inadequate response[e] at month 3 were switched to the respective double-blind active extension arm, the switch to tofacitinib 5 mg or 10 mg took place at month 6 at the latest.
e: Inadequate response after 3 months is defined as lack of improvement by at least 20% in both tender joint count (TJC) and swollen joint count (SJC) compared with the start of the study.

ACR20: American College of Rheumatology; AE: adverse event; bid: twice daily; cDMARD: conventional disease-modifying antirheumatic drug; DAS28: Disease-Activity-Score-28; ESR: erythrocyte sedimentation rate; Gr.: group; HAQ-DI: Health Assessment Questionnaire-Disability Index; MTX: methotrexate; n: relevant subpopulation; N: number of randomized (included) patients; RCT: randomized controlled trial; SJC: swollen joint count; TJC: tender joint count; TNFi: tumour necrosis factor inhibitor; vs.: versus

Table 8: Characterization of the intervention – RCT, direct comparison: tofacitinib + MTX versus adalimumab + MTX

Study	Intervention	Comparison
ORAL STANDARD	Tofacitinib 5 mg orally, twice/day (morning and evening at 12-hour intervals) for 12 months + Placebo subcutaneously (injections), every 2 weeks for 12 months	Adalimumab 40 mg subcutaneously, every 2 weeks for 12 months + Placebo orally (tablets), twice/day (morning and evening at 12-hour intervals) for 12 months
	Prior and concomitant medication: ▪ MTX: continuation of the oral or parenteral MTX therapy having been maintained for ≥ 4 months, ≥ 6 weeks at a stable dose (7.5–25 mg/week) prior to the administration of the first study medication ▪ nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics[a] and oral corticosteroids (≤ 10 mg prednisone or equivalent): allowed at a stable dose ≥ 4 weeks prior to the first study medication; the dose could be adjusted for safety reasons ▪ i.a. corticosteroids were allowed as of the study visit at month 6 (in ≤ 2 joints) **Non-permitted concomitant medication:** ▪ intravenous and intramuscular corticosteroids, biologics[b] and DMARDs (excl. MTX)[b]	

a: The following total doses were not to be exceeded: paracetamol: ≥ 2.6 g/day; opiates: ≥ 30 mg/day, morphine (orally); administration as rescue therapy was possible on ≤ 10 consecutive days, otherwise, the study had to be discontinued; no administration 24 hours before a study visit.
b: Biologics and DMARDs (excl. MTX) had to be discontinued 4 to 12 weeks or 1 year (rituximab) before the start of the study.
DMARDs: conventional disease-modifying antirheumatic drug; excl.: excluding, i. a.: intraarticular; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; vs.: versus

The ORAL STANDARD study was a randomized, multicentre, double-blind, parallel-group phase 3 study. The study included adult patients with active rheumatoid arthritis and inadequate response to MTX.

A total of 717 patients were randomly allocated to the arms tofacitinib 5 mg bid + MTX (204 patients), tofacitinib 10 mg bid + MTX (201 patients), adalimumab + MTX (204 patients) and placebo + MTX (2 placebo arms with 56 and 52 patients respectively). For the present assessment, only the study arms tofacitinib 5 mg bid + MTX as well as adalimumab + MTX are relevant, therefore, the subsequent description only refers to these two study arms.

In the intervention arm, tofacitinib was administered twice daily orally as 5 mg tablet, which is in compliance with the approval; subcutaneous placebo injection was administered every 2 weeks. In the comparator arm, adalimumab was administered as subcutaneous injection every 2 weeks, which is in compliance with the approval; placebo was administered as a tablet twice daily orally.

Patients could receive concomitant analgesic therapy with paracetamol (up to 2.6 g/day) or opioids (up to 30 mg or equivalent) for a maximum of 10 consecutive days.

The planned treatment period was 12 months.

Primary outcome of the ORAL STANDARD study was the 20% improvement in American-College-of-Rheumatology (ACR) criteria (ACR20) from the start of the study until week 24. Patient-relevant outcomes on morbidity, health-related quality of life and AEs were additionally recorded.

Relevant subpopulation for research question 2

The subpopulation of patients with poor prognostic factors and inadequate response to prior treatment with 1 cDMARD was relevant for research question 2. Hence, the relevant subpopulation of the ORAL STANDARD study comprised patients who showed inadequate response only to the cDMARD MTX (for prognostic factors of the patients, see section on patient characteristics). This relevant subpopulation comprised 81 patients in the intervention arm and 76 patients in the comparator arm.

For the relevant subpopulation, the company provided results for the data cut-off at month 12.

Patient characteristics

Table 9 shows the characteristics of the patients in the relevant subpopulation of the study included.

Table 9: Characteristics of the included study population – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 2)

Study Characteristics Category	**Tofacitinib + MTX**	**Adalimumab + MTX**
ORAL STANDARD	N[a] = 81	N[a] = 76
Age [years], mean (SD)	55 (13)	52 (12)
Sex [F/M], %	84/16	84/16
Region, n (%)		
Europe	42 (51.9)	41 (53.9)
USA/Canada	19 (23.5)	13 (17.1)
Latin America	11 (13.6)	10 (13.2)
other	9 (11.1)	12 (15.8)
Disease duration: time between first diagnosis and randomization [years], mean (SD)	5.1 (6.7)	5.1 (6.4)
Functional status [HAQ-DI], mean (SD)	1.4 (0.6)	1.6 (0.6)
Tender joint count[b], mean (SD)	30.2 (16.0)	28.6 (16.2)
Swollen joint count[c], mean (SD)	16.3 (8.8)	15.9 (8.2)
Rheumatoid factor status, n (%)		
Positive	51 (63.0)	47 (61.8)
Negative	26 (32.1)	27 (35.5)
Unknown	4 (4.9)	2 (2.6)
ACPA status, n (%)		
Positive	49 (60.5)	56 (73.7)
Negative	31 (38.3)	20 (26.3)
Unknown	1 (1.2)	0 (0)
DAS28-4 ESR, n (%)		
< 2.6	0 (0)	0 (0)
2.6-3.2	0 (0)	0 (0)
> 3.2 – ≤ 5.1	6 (7.4)	5 (6.6)
> 5.1	71 (87.7)	67 (88.2)
Unknown	4 (4.9)	4 (5.3)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation[d], n (%)	ND	ND

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Based on 68 joints.
c: Based on 66 joints.
d: Study discontinuation in the total study population: tofacitinib n = 54 (26%) of 204; adalimumab n = 42 (21%) of 204.

ACPA: anti-citrullinated protein antibody; DAS28: Disease-Activity-Score-28; ESR: erythrocyte sedimentation rate; f: female; HAQ-DI: Health Assessment Questionnaire-Disability Index; m: male; n: number of patients in the category; N: number of randomized (or included) patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Overall, the patient characteristics between the arms of the ORAL STANDARD study in the relevant subpopulation were balanced. The mean age of the patients was about 54 years. Markedly more women (84%) than men were included in both arms, reflecting the higher prevalence of rheumatoid arthritis in women (5, 6).

A majority of patients was seropositive (positive rheumatoid factor serostatus and/or positive anti-citrullinated peptide antibodies [ACPA] serostatus). All patients had moderate to high disease activity (Disease Activity Score 28-4-erythrocyte sedimentation rate [DAS28-4 ESR] > 3.2). The distribution of the disease characteristics shows that patients in both study arms were patients with poor prognostic factors.

There was no information on study discontinuations for the relevant subpopulation.

Risk of bias at study level

Table 10 shows the risk of bias at study level.

Table 10: Risk of bias at study level – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX

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

The risk of bias at study level was rated as low for the ORAL STANDARD study. This corresponds to the company's assessment.

2.5.2 Results on added benefit (research question 2)

2.5.2.1 Outcomes included (research question 2)

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

- Mortality
  - All-cause mortality
- Morbidity
  - remission
  - low disease activity
  - Tender joints
  - swollen joints
  - pain, measured using a VAS
  - disease activity, measured using a VAS
  - fatigue, measured using the Functional Assessment of Chronic Illness Therapy ([FACIT]-Fatigue)
  - physical functioning, measured using the HAQ-DI
  - Sleep disturbances, measured using the MOS sleep scale
- Health-related quality of life
  - measured with the physical and mental component summary of the SF-36v2 acute
- Side effects
  - Serious adverse event (SAE)
  - discontinuation due to AEs
  - infections
  - serious infections
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviates from that of the company (see Section 2.9.2.4.3 of the full dossier assessment).

Table 11 shows for which outcomes data were available for the relevant subpopulation of the study included.

Table 11: Matrix of outcomes – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 2)

Study	Outcomes														
	All-cause mortality	**Remission (CDAI ≤ 2.8)**	**Low disease activity (DAS28-4 ESR ≤ 3.2)**	**Tender joints[a]**	**swollen joints[a]**	**pain (VAS)**	**Disease activity (VAS)**	**Fatigue (FACIT-Fatigue)**	**Physical functioning (HAQ-DI)**	**Sleep disturbances (MOS sleep scale)**	**Health-related quality of life (SF-36v2 acute)**	**SAEs**	**Discontinuation due to AEs**	**Infections[b]**	**Serious infections**
ORAL STANDARD	No[c]	Yes	Yes	Yes	Yes	No[d]	No[d]	Yes	Yes	No[d]	Yes	Yes	Yes	Yes	No[c]

a: Based on 28 joints.
b: Any AEs of the SOC "infections and infestations".
c: The company presented no data for the subpopulation.
d: The available data were not usable, see Section 2.9.2.4.3 of the full dossier assessment for reasons.

AE: adverse event; CDAI: Clinical Disease Activity Index; DAS28: Disease-Activity-Score-28; ESR: erythrocyte sedimentation rate; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; MOS: Medical Outcome Study; MTX: methotrexate; RCT: randomized controlled trial; SF-36v2: Short Form 36 – version 2 Health Survey; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2.2 Risk of bias (research question 2)

Table 12 shows the risk of bias for the relevant outcomes.

Table 12: Risk of bias at study and outcome level – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 2)

Study		Outcomes														
	Study level	All-cause mortality	Remission (CDAI ≤ 2.8)	Low disease activity (DAS28-4 ESR ≤ 3.2)	Tender joints	swollen joints[a]	pain (VAS)	disease activity (VAS)	Fatigue (FACIT-Fatigue)	Physical functioning (HAQ-DI)	Sleep disturbances (MOS sleep scale)	Health-related quality of life (SF-36v2 acute)	SAEs	Discontinuation due to AEs	Infections[b]	Serious infections
ORAL STANDARD	N	-[c]	H[d]	H[d]	H[d]	H[d]	–[e]	–[e]	H[d]	H[d]	–[e]	H[d]	H[f]	N	H[f]	-[c]

a: Based on 28 joints.
b: Any AEs of the SOC "infections and infestations".
c: The company did not present data for the subpopulation.
d: Large proportion of values imputed (> 15%).
e: The available data were not usable, see Section 2.9.2.4.3 of the full dossier assessment for reasons.
f: Unclear proportion of patients who were not completely observed.

AE: adverse event; CDAI: Clinical Disease Activity Index; DAS28: Disease-Activity-Score-28; ESR: erythrocyte sedimentation rate; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; H: high; HAQ-DI: Health Assessment Questionnaire-Disability Index; MOS: Medical Outcome Study; MTX: methotrexate; L: low; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36 – version 2 Health Survey; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

Concurring with the company's assessment, the risk of bias for the outcome "discontinuation due to AEs" was rated as low. The assessment of the risk of bias for the outcome DAS28-4 ESR as high also corresponds to the rating of the company. Unlike the company, the risk of bias was rated as high for all further outcomes for which analyses were available for the relevant subpopulation.

The risk of bias was rated as high for all outcomes on morbidity and health-related quality of life, because the proportion of values imputed is > 15% and the intention-to-treat (ITT) principle was therefore not adequately implemented. The high risk of bias for the AE outcomes "SAEs" and "infections" resulted from the unclear proportion of not completely observed patients.

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

2.5.2.3 Results (research question 2)

Table 13 and Table 14 summarize the results of the comparison of tofacitinib + MTX with adalimumab + MTX in patients with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with 1 cDMARD and poor prognostic factors. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations.

Table 13: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 2)

Study Outcome category Outcome	Tofacitinib + MTX		Adalimumab + MTX		Tofacitinib + MTX vs. adalimumab + MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
ORAL STANDARD					
Mortality					
All-cause mortality	79	0 (0)	75	ND[b]	–
Morbidity – proportion of patients with improvement					
Remission (CDAI ≤ 2.8)[c]	79	12 (15.2)	75	7 (9.3)	1.63 [0.68; 3.91]; < 0.288
low disease activity DAS28-4 ESR ≤ 3.2[d]	70	16 (22.9)	64	19 (29.7)	0.77 [0.43; 1.36]; < 0.530
tender joints[e](≤ 1)	79	24 (30.4)	75	22 (29.3)	1.04 [0.64; 1.68]; < 0.922
swollen joints[e](≤ 1)	79	36 (45.6)	75	34 (45.3)	1.01 [0.71; 1.42]; > 0.999
Fatigue (FACIT-Fatigue)[f]	79	37 (46.8)	75	41 (54.7)	0.86 [0.63; 1.17]; < 0.515
Physical functioning (HAQ-DI)[g]	79	49 (62.0)	75	49 (65.3)	0.95 [0.75; 1.21]; < 0.718
Side effects					
AEs (supplementary information)	83	61 (73.5)	78	53 (67.9)	–
SAEs	83	13 (15.7)	78	4 (5.1)	3.05 [1.04; 8.97]; < 0.030
Discontinuation due to AEs	83	8 (9.6)	78	5 (6.4)	1.50 [0.51; 4.40]; < 0.532
Infections[h]	83	35 (42.2)	78	25 (32.1)	1.32 [0.87; 1.98]; < 0.224
serious infections	No usable data				

a: Institute's calculation, unconditional exact test (CSZ method according to [7].
b: At most 1 patient in the adalimumab arm, it is unclear whether death occurred in this subpopulation.
c: Further remission criteria, n (%):
- SDAI ≤ 3.3: tofacitinib + MTX (N = 79): 12 (15.2) vs. adalimumab + MTX (N = 75): 6 (8.0)
- American-College-of-Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria (Boolean definition): tofacitinib + MTX (N = 79): 7 (8.9) vs. adalimumab + MTX (N = 75): 4 (5.3).

d: Results, n (%) DAS28-4 CRP ≤ 3.2: tofacitinib + MTX (N = 79): 40 (50.6) vs. adalimumab + MTX (N = 75): 34 (45.3).
e: Based on 28 joints.
f: Patients with improvement by ≥ 4 points.
g: Patients with improvement by ≥ 0.22 points.
h: Any AEs of the SOC "infections and infestations".

ACR: American College of Rheumatology; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: Disease-Activity-Score-28; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; 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; ND: no data; RCT: randomized controlled trial; SDAI: Simplified Disease Activity Index; SAE: serious adverse event; AE: adverse event; vs.: versus

Table 14: Results (morbidity and health-related quality of life, continuous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 2)

Study Outcome category Outcome	Tofacitinib + MTX			Adalimumab + MTX			Tofacitinib + MTX vs. adalimumab + MTX
	N[a]	Values at start of study mean (SD)	Change at end of study mean (SD)	N[a]	Values at start of study mean (SD)	Change at end of study mean (SD)	MD [95% CI]; p-value[b]
ORAL STANDARD							
Morbidity							
Pain (VAS)	No usable data						
disease activity (VAS)	No usable data						
Sleep disturbances (MOS sleep scale)	No usable data						
Health-related quality of life							
SF-36v2 acute[c]							
Physical sum score	79	33.3 (7.76)	8.2 (8.42)[d]	75	31.8 (6.46)	9.0 (7.92)[d]	0.91 [−1.58; 3.41]; 0.472
Mental sum score	79	39.7 (12.83)	4.3 (9.02)[d]	75	39.9 (11.58)	3.6 (11.19)[d]	0.81 [−2.22; 3.84]; 0.597

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: From a mixed-effects model repeated measures (MMRM) (fixed effects: treatment, time point of the study, treatment × time point of the study, region, baseline value; random effect: patient).
c: Higher values indicate improvement.
d: Based on patients for whom values were available at month 12, N = 59 (73) vs. N = 61 (77).
MMRM: mixed-effects model repeated measures; MOS: Medical Outcome Study; MTX: Methotrexate; MW: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SF-36v2: Short Form 36 –version 2 Health Survey; VAS: visual analogue scale; vs.: versus

One relevant study was available for the assessment of the added benefit of tofacitinib. In view of the low risk of bias, at most an indication of an added benefit can be derived for the outcome “discontinuation due to AEs”. For all other outcomes, at most hints of an added benefit can be derived due to the high risk of bias (see Section 2.5.2.2, and Section 2.9.2.4.2 of the full dossier assessment).

This partly deviates from the assessment of the company, which rated the risk of bias as low for most outcomes and therefore considered the derivation of an indication of an added benefit for all outcomes to be justified.

Mortality

All-cause mortality

There were no usable data for the outcome “all-cause mortality” for the subpopulation. Only 1 patient of the total study population died during the observation period in the relevant study

arms, namely in the adalimumab arm. This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company insofar as the company did not use the outcome "all-cause mortality" in its assessment.

Morbidity

Remission

No statistically significant difference between the treatment groups was shown for the outcome "remission" (Clinical Disease Activity Index [CDAI] ≤ 2.8). This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This corresponds to the company's assessment which also derived no added benefit for the outcome "remission" (operationalized using several remission criteria, e.g., DAS28-4 < 2.6; CDAI ≤ 2.8; SDAI ≤ 3.3 and the Boolean definition according to the ACR/EULAR).

Low disease activity

No statistically significant difference between the treatment groups was shown for the outcome "low disease activity" (DAS28-4 ESR ≤ 3.2). This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company, which also derived no added benefit for the outcome "low disease activity" (operationalized using the achievement of several criteria, e.g., DAS28-4 ESR ≤ 3.2; DAS28-4 C-reactive protein [CRP] ≤ 3.2; CDAI ≤ 10, SDAI ≤ 11).

Tender joints and swollen joints

No statistically significant difference between the treatment groups was shown for the outcomes "tender joints" and "swollen joints" for the number of responders (≤ 1 tender / swollen joint). This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for these outcomes; an added benefit is therefore not proven.

This concurs with the assessment of the company, which also claimed no added benefit for the outcomes "tender joints" and "swollen joints".

Pain (VAS)

The company presented no usable data for the outcome "pain (VAS)". This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

In addition, the company used analyses of the proportions of patients with a VAS improvement by ≥ 10 mm in its assessment. This response criterion was considered to be unvalidated (see Section 2.9.2.4.3 of the full dossier assessment). On the basis of the responder analyses, the company also derived no added benefit.

Disease activity (VAS)

The company presented no usable data for the outcome "disease activity" (VAS). This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

In addition, the company used analyses of the proportions of patients with a VAS improvement by ≥ 10 mm in its assessment. This response criterion was considered to be unvalidated (see Section 2.9.2.4.3 of the full dossier assessment). On the basis of the responder analyses, the company also derived no added benefit.

Fatigue (FACIT-Fatigue)

No statistically significant difference between the treatment groups was shown for the number of responders (improvement ≥ 4) for the outcome "Fatigue" (FACIT-Fatigue). This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company, which also claimed no added benefit for the outcome "Fatigue" (FACIT-Fatigue).

Physical functioning (HAQ-DI)

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

This concurs with the assessment of the company, which also claimed no added benefit for the outcome "physical functioning" (HAQ-DI). The company considered analyses on the different response criteria of an improvement by ≥ 0.22, ≥ 0.3 and ≥ 0.5.

Sleep disturbances (MOS sleep scale)

There were no usable data for the outcome "sleep disturbances" (MOS sleep scale) (see Section 2.9.2.4.3of the full dossier assessment). This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

The company also derived no added benefit for the outcome "sleep disturbances" (MOS sleep scale).

Health-related quality of life

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

For the physical and the mental component summary of the SF-36v2 acute, no statistically significant difference between the treatment groups was shown for the mean change. This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for these outcomes; an added benefit is therefore not proven.

This deviates from the company's assessment insofar as the company considered responder analyses based on a minimally important difference (MID) ≥ 2.5 when deriving an added benefit. This response criterion was considered to be unvalidated (see Section 2.9.2.4.3 of the full dossier assessment). However, the company also claimed no added benefit on the basis of the responder analyses.

Side effects

SAEs

A statistically significant difference to the disadvantage of tofacitinib + MTX was shown for the outcome "SAEs". Moreover, there was an effect modification by the characteristic "age" for this outcome (see Section 2.5.2.4 of the full dossier assessment). For patients ≤ 65 years, this resulted in a hint of greater harm of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome. For patients > 65 years, this resulted in no hint of greater or lesser harm from tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; greater or lesser harm is therefore not proven for patients > 65 years.

This is largely in accordance with the company's assessment at outcome level, which, however, rated the certainty of results as "indication". Therefore, the company derived an indication of a lesser benefit for patients ≤ 65 years.

Discontinuation due to AEs and infections

No statistically significant difference between the treatment groups was shown for the outcomes "discontinuation due to AEs" and "infections (AEs of the System Organ Class [SOC] "infections and infestations"). Hence, for these outcomes, there was no hint of greater or lesser harm from tofacitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven.

This corresponds to the company's assessment.

Serious infections

There were no usable data on the outcome serious infections for the relevant subpopulation, because the company had not analysed this prespecified outcome for the subpopulations (see Section 2.9.2.4.3 of the full dossier assessment). Table 31 and Table 32 in Appendix A show information on SAEs of the SOC "infections and infestations" as well as a list of the SAEs for

the total population of the ORAL STANDARD study. These analyses show that a relevant proportion of the SAEs were infections.

Given the missing data for this outcome, there was altogether no hint of greater or lesser harm from tofacitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven.

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

2.5.2.4 Subgroups and other effect modifiers (research question 2)

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

- sex (men/women)
- age (≤ 65/> 65 years)
- region (Europe / rest of the world)
- disease activity at the start of the study based on the DAS28-4 ESR (≤ 5.1/> 5.1)

For most outcomes included, the company presented subgroup analyses for the relevant subpopulation.

The company presented no subgroup analyses on the outcomes "all-cause mortality" and "serious infections", since it does not include these outcomes in its assessment.

For the remaining outcomes, only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) (see Section 2.9.2.2 of the full dossier assessment) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least 1 subgroup.

Table 15 summarizes the subgroup analyses of the comparison of tofacitinib + MTX with adalimumab + MTX in patients with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with 1 cDMARD and poor prognostic factors. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations.

Table 15: Subgroups (side effects) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 2)

Study Outcome	Tofacitinib + MTX		Adalimumab + MTX		Tofacitinib + MTX vs. adalimumab + MTX	
Characteristic Subgroup	N	Patients with event n (%)	N	Patients event n (%)	RR [95% CI]	p-value
ORAL STANDARD						
Age						
≤ 65	64	12 (18.8)	66	2 (3.0)	6.19 [1.44; 26.56]	0.004[a]
> 65	19	1 (5.3)	12	2 (16.7)	0.32 [0.03; 3.12]	0.409[a]
Total					Interaction:	0.032

a: Institute's calculation, unconditional exact test (CSZ method according to [7].

CI: confidence interval; MTX: methotrexate; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Side effects

SAEs

There was an effect modification by the characteristic "age" for the outcome "SAEs".

A statistically significant difference to the disadvantage of tofacitinib + MTX was shown for patients ≤ 65 years. This resulted in a hint of a greater harm of tofacitinib + MTX in comparison with adalimumab + MTX for patients ≤ 65 years. There was no statistically significant difference between the treatment groups for patients > 65 years. For patients > 65 years, this resulted in no hint of greater or lesser harm from tofacitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven for patients > 65 years.

This resulted in a hint of greater harm of tofacitinib + MTX in comparison with adalimumab + MTX for the outcome "SAEs" for patients ≤ 65 years.

This is largely in accordance with the company's assessment at outcome level, which, however, rated the certainty of results as "indication". Therefore, the company derived an indication of a lesser benefit for patients ≤ 65 years.

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

The probability and extent of added benefit for patients with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with 1 cDMARD and poor prognostic factors were derived at outcome level. The different outcome categories and the effect sizes are taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [8].

This procedure for deriving an overall conclusion on the added benefit based on the aggregation of the conclusions deduced at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

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

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

- a hint of greater harm regarding SAEs for patients ≥ 65 years.

The extent of the respective added benefit at outcome level was estimated from this result (see Table 16).

Table 16: Extent of added benefit at outcome level: tofacitinib + MTX vs. adalimumab + MTX (research question 2)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Tofacitinib + MTX vs. adalimumab + MTX** **Proportion of patients with event or change** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	Proportion: 0% vs. no data[c]	Lesser benefit/added benefit not proven
Morbidity		
Remission (CDAI ≤ 2.8)[d]	Proportion: 15.2% vs. 9.3% RR: 1.63 [0.68; 3.91]; p = 0.288	Lesser benefit/added benefit not proven
Low disease activity (DAS28-4 ESR ≤ 3.2)[e]	Proportion: 22.9% vs. 29.7% RR: 0.77 [0.43; 1.36]; p = 0.530	Lesser benefit/added benefit not proven
tender joints (≤ 1)	Proportion: 30.4% vs. 29.3% RR: 1.04 [0.64; 1.68]; p = 0.922	Lesser benefit/added benefit not proven
swollen joints (≤ 1)	Proportion: 45.6% vs. 45.3% RR: 1.01 [0.71; 1.42]; p < 0.999	Lesser benefit/added benefit not proven
Pain (VAS)	No usable data[f]	Lesser benefit/added benefit not proven
Disease activity (VAS)	No usable data[f]	Lesser benefit/added benefit not proven
Fatigue (FACIT-F)[g]	Proportion: 46.8% vs. 54.7% RR: 0.86 [0.63; 1.17]; p = 0.515	Lesser benefit/added benefit not proven
physical functioning (HAQ-DI)[h]	Proportion: 62.0% vs. 65.3% RR: 0.95 [0.75; 1.21]; p = 0.718	Lesser benefit/added benefit not proven
Sleep disturbances (MOS sleep scale)	No usable data[f]	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36v2 acute		
Physical sum score	Mean change between start of the study and month 12: 8.2 vs. 9.0 MD: 0.91 [−1.58; 3.41]; p = 0.472	Lesser benefit/added benefit not proven
Mental sum score	Mean change between start of the study and month 12: 4.3 vs. 3.6 MD: 0.81 [−2.22; 3.84]; p = 0.597	Lesser benefit/added benefit not proven

(continued)

Table 16: Extent of added benefit at outcome level: tofacitinib + MTX vs. adalimumab + MTX (research question 2) (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Tofacitinib + MTX vs. adalimumab + MTX** **Proportion of patients with event or change** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs Age		
≤ 65 years	Proportion: 18.8% vs. 3.0% RR: 6.19 [1.44; 26.56] RR[i]: 0.16 [0.04; 0.69]; p = 0.004 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: "major"
> 65 years	Proportion: 5.3% vs. 16.7% RR: 0.32 [0.03; 3.12]; p = 0.409	Greater/lesser harm not proven
Discontinuation due to AEs	Proportion: 9.6% vs. 6.4% RR: 1.50 [0.51; 4.40]; p = 0.532	Greater/lesser harm not proven
Infections	Proportion: 42.2% vs. 32.1% RR: 1.32 [0.87; 1.98]; p = 0.224	Greater/lesser harm not proven
serious infections	no usable data[j]	Greater/lesser harm not proven

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: At most 1 patient in the adalimumab arm.
d: The results of the other remission criteria SDAI ≤ 3.3 and according to ACR/EULAR are consistent.
e: The results for the operationalization as DAS28-4 CRP ≤ 3.2 are consistent.
f: No usable data for the relevant subpopulation available; see Section 2.9.2.4.3 of the full dossier assessment for reasons.
g: Patients with improvement by ≥ 4 points.
h: Patients with improvement by ≥ 0.22 points.
i: Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
j: The company presented no analyses for the relevant subpopulation for this outcome.
ACR American College of Rheumatology; AE: adverse event; CDAI: Clinical Disease Activity Index; CI: confidence interval; DAS28: Disease-Activity-Score-28; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; MOS: Medical Outcome Study; MTX: methotrexate; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SDAI: Simplified Disease Activity Index; VAS: visual analogue scale; vs.: versus.

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

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

Table 17: Positive and negative effects from the assessment of tofacitinib + MTX in comparison with adalimumab + MTX (research question 2)

Positive effects	Negative effects
–	serious/severe side effects ▪ SAEs: ▫ age (≤ 65 years): hint of greater harm – extent: "major"
MTX: methotrexate; SAE serious AEs	

The results showed an effect modification by age for the outcome "SAEs". Hereinafter, the overall conclusion on the added benefit is derived separately for patients ≤ 65 years and for patients > 65 years.

Patients ≤ 65 years

Overall, only a negative effect was found for patients ≤ 65 years. There was one hint of greater harm with the extent "major" in the category "serious/severe side effects (SAEs)".

Hence, there is a hint of lesser benefit of tofacitinib in comparison with adalimumab for patients ≤ 65 with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with 1 cDMARD and with poor prognostic factors.

Patients > 65 years

In summary, there are neither positive nor negative effects for patients > 65 years. This resulted in no hint of an added benefit of tofacitinib in comparison with the ACT for patients > 65 years with moderate to severe active rheumatoid arthritis who have responded inadequately to prior treatment with one cDMARDs and with poor prognostic factors. An added benefit is therefore not proven.

The result of the assessment of the added benefit of tofacitinib in comparison with the ACT for patients with inadequate response to 1 cDMARD and with poor prognostic factors is summarized in Table 18.

Table 18: Tofacitinib – probability and extent of added benefit (research question 2)

Therapeutic indication	ACT[a]	Subgroup	Probability and extent of added benefit
Patients with poor prognostic factors[b] who have responded inadequately to prior treatment with 1 conventional disease-modifying antirheumatic drug (DMARD)[c].	Biologic disease-modifying antirheumatic drug (bDMARD) in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance	≤ 65 years	Hint of lesser benefit
		> 65 years	Added benefit not proven

a: Presentation of the appropriate comparator therapy specified by the G-BA. In cases where the pharmaceutical company (hereinafter referred to as "the company"), because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Poor prognostic factors: detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.
c: According to the SPC, tofacitinib is also approved for patients who have not tolerated prior treatment with a DMARD [3]. The relevant subpopulation of the included study for the assessment of the added benefit (only patients who have shown inadequate response to MTX) therefore does not completely cover the therapeutic indication. It remains unclear whether the observed effects can be transferred to patients who have not tolerated prior treatment with a DMARD.
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DAS: Disease Activity Score; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate; SPC: Summary of Product Characteristics

This approach deviated from that of the company which overall derived no added benefit for patients of research question 2 and rated the effect regarding the SAEs as irrelevant (see also Section 2.9.2.3 of the full dossier assessment).

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

2.5.4 List of included studies (research question 2)

Pfizer. Phase 3 randomized, double-blind, active comparator, placebo-controlled study of the efficacy and safety of 2 doses of CP 690,550 in patients with active rheumatoid arthritis on background methotrexate [online]. In: EU Clinical Trials Register. [Accessed: 31.05.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-008338-35.

Pfizer. A phase 3 study comparing 2 doses of CP-690,550 and the active comparator, Humira (adalimumab) vs. placebo for treatment of rheumatoid arthritis: full text view [online]. In: ClinicalTrials.gov. 10.01.2013 [Accessed: 31.05.2017]. URL: https://ClinicalTrials.gov/show/NCT00853385.

Pfizer. Phase 3 randomized, double-blind, active comparator, placebo-controlled study of the efficacy and safety of 2 doses of CP-690,550 in patients with active rheumatoid arthritis on background methotrexate: public disclosure synopsis [online]. In: EU Clinical Trials Register. 24.11.2014 [Accessed: 10.07.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/rest/download/result/attachment/2008-008338-35/1/13973

Pfizer. A phase 3 study comparing 2 doses of CP-690,550 and the active comparator, Humira (adalimumab) vs. placebo for treatment of rheumatoid arthritis: study results [online]. In: ClinicalTrials.gov. 10.01.2013 [Accessed: 31.05.2017]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00853385.

Pfizer. Phase 3 randomized, double-blind, active comparator, placebo-controlled study of the efficacy and safety of 2 doses of CP-690,550 in patients with active rheumatoid arthritis on background methotrexate: study A3921064; statistical analysis plan [unpublished]. 2010.

Pfizer. Phase 3 randomized, double-blind, active comparator, placebo-controlled study of the efficacy and safety of 2 doses of CP-690,550 in patients with active rheumatoid arthritis on background methotrexate: study A3921064; final amendment 3 [unpublished]. 2011.

Pfizer. Phase 3 randomized, double-blind, active comparator, placebo-controlled study of the efficacy and safety of 2 doses of CP-690,550 in patients with active rheumatoid arthritis on background methotrexate: study A3921064; full clinical study report [unpublished]. 2014.

Pfizer. Phase 3 randomized, double-blind, active comparator, placebo-controlled study of the efficacy and safety of 2 doses of CP-690,550 in patients with active rheumatoid arthritis on background methotrexate: study A3921064; Zusatzanalysen [unpublished]. 2017.

Strand V, Van Vollenhoven RF, Lee EB, Fleischmann R, Zwillich SH, Gruben D et al. Tofacitinib or adalimumab versus placebo: patient-reported outcomes from a phase 3 study of active rheumatoid arthritis. Rheumatology (Oxford) 2016; 55(6): 1031-1041.

Van Vollenhoven R, Cohen S, Mendelsohn A, Bananis E, Fan H, Takiya L et al. AB0398 efficacy of adalimumab and tofacitinib in rheumatoid arthritis: post-hoc analyses from a phase 3 study. Ann Rheum Dis 2016; 75: 1042.

Van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012; 367(6): 508-519.

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

2.6.1 Study characteristics (research question 3)

The study used for the benefit assessment with the subpopulation relevant for the present research question is described in Table 19.

Table 19: Characteristics of the study included – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 3)

Study	Study design	Population	Interventions (number of randomized patients)	Study Duration	Location and period of study	Primary outcome; secondary outcomes[a]
ORAL STANDARD	RCT, double-blind, parallel	Adult patients with active rheumatoid arthritis and ▪ inadequate response under treatment with MTX ▪ continuous administration of MTX for ≥ 4 months and in stable doses of 7.5 mg to 25 mg per week ≥ 6 weeks before the first administration of the study medication ▪ no treatment failure under tumour necrosis factor inhibitor (TNFi) and no specific AEs following the intake of TNFi	Each in combination with MTX: tofacitinib 5 mg bid (N = 204) tofacitinib 10 mg bid (N = 201)[b] placebo → tofacitinib 5 mg bid (N = 56)[b] placebo → tofacitinib 10 mg bid (N = 52)[b] adalimumab 40 mg (N = 204) Relevant analysed subpopulation thereof[c]: tofacitinib 5 mg bid (N = 102) adalimumab 40 mg (N = 104)	Screening: 1 month Treatment: 12 months[d] Follow-up: 28 days after the last administration of the study medication (safety)	115 centres in Australia, Bosnia and Herzegovina, Bulgaria, Canada, Chile, Costa Rica, Croatia, Czech Republic, Denmark, Dominican Republic, Finland, Germany, Korea, Mexico, Philippines, Poland, Slovak Republic, Spain, Thailand, USA, United Kingdom 05/2009-03/2011	Primary: ▪ ACR20 at month 6 ▪ HAQ-DI at month 3 ▪ DAS28-4 ESR < 2.6 at month 6 Secondary: ▪ Morbidity ▪ health-related quality of life ▪ AEs

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: The study arm is not relevant for the assessment and is not shown in the next tables.
c: Patients who have responded inadequately to prior treatment with several cDMARDs.
d: During the 6-month double-blind placebo-controlled study phase all patients from the two placebo arms with unadequate response[e] at month 3 were switched to the respective double-blind active extension arm, the switch to tofacitinib 5 mg or 10 mg took place at month 6 at the latest.
e: Inadequate response after 3 months is defined as lack of improvement by at least 20% in both tender joint count (TJC) and swollen joint count (SJC) compared with the start of the study.

ACR20: American College of Rheumatology; bid: twice daily; cDMARD: conventional disease-modifying antirheumatic drug; DAS28: Disease-Activity-Score-28; ESR: erythrocyte sedimentation rate; Gr.: group; HAQ-DI: Health Assessment Questionnaire-Disability Index; MTX: methotrexate; N: number of randomized (included) patients; RCT: randomized controlled trial; SJC: swollen joint count; TJC: tender joint count; TNFi: tumour necrosis factor inhibitor; AE: adverse event; vs.: versus

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

Relevant subpopulation for research question 3

For research question 3, the subpopulation of patients in the ORAL STANDARD study with inadequate response to prior treatment with several cDMARDs was relevant. The relevant subpopulation comprised 102 patients in the intervention arm and 104 patients in the comparator arm.

Patient characteristics

Table 20 shows the characteristics of the patients in the relevant subpopulation of the study included.

Table 20: Characteristics of the included study population – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 3)

Study Characteristics Category	**Tofacitinib + MTX**	**Adalimumab + MTX**
ORAL STANDARD	N[a] = 102	N[a] = 104
Age [years], mean (SD)	52 (11)	53 (11)
Sex [F/M], %	87/13	75/25
Region, n (%)		
Europe	64 (62.7)	61 (58.7)
USA/Canada	9 (8.8)	11 (10.6)
Latin America	7 (6.9)	11 (10.6)
other	22 (21.6)	21 (20.2)
Disease duration: time between first diagnosis and randomization [years], mean (SD)	9.2 (7.6)	10.1 (7.5)
Functional status [HAQ-DI], mean (SD)	1.5 (0.6)	1.5 (0.6)
Tender joint count[b], mean (SD)	27.4 (14.3)	25.0 (14.4)
Swollen joint count[c], mean (SD)	17.0 (9.0)	16.3 (8.5)
Rheumatoid factor status, n (%)		
Positive	70 (68.6)	74 (71.2)
Negative	32 (31.4)	30 (28.8)
ACPA status, n (%)		
Positive	82 (80.4)	79 (76.0)
Negative	20 (19.6)	24 (23.1)
Unknown	0 (0)	1 (1.0)
DAS28-4 ESR, n (%)		
< 2.6	0 (0)	0 (0)
2.6-3.2	0 (0)	0 (0)
> 3.2 –≤ 5.1	4 (3.9)	10 (9.6)
> 5.1	96 (94.1)	91 (87.5)
Unknown	2 (2.0)	3 (2.9)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation[d], n (%)	ND	ND

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Based on 68 joints.
c: Based on 66 joints.
d: Study discontinuation in the total study population: tofacitinib n = 54 (26%) of 204; adalimumab n = 42 (21%) of 204

ACPA: anti-citrullinated peptide antibody; DAS28: Disease-Activity-Score-28; ESR: erythrocyte sedimentation rate; f: female; HAQ-DI: Health Assessment Questionnaire-Disability Index; m: male; ND: no data; n: number of patients in the category; N: number of randomized (or included) patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus.

Overall, the patient characteristics between the arms of the ORAL STANDARD study in the relevant subpopulation were balanced. The mean age of the patients was about 53 years. Markedly more women (75% to 87%) than men were included in both arms, reflecting the higher prevalence of rheumatoid arthritis in women [5,6].

A majority of patients was seropositive (positive rheumatoid factor and/or positive ACPA serostatus). All patients had moderate to high disease activity (DAS28-4 ESR > 3.2). The distribution of the disease characteristics shows that patients in both study arms were patients with poor prognostic factors.

There was no information on study discontinuations for the relevant subpopulation.

Risk of bias at study level

The risk of bias at study level was rated as low for the ORAL STANDARD study (see Table 10in Section 2.5.1). This corresponds to the company's assessment.

2.6.2 Results on added benefit (research question 3)

2.6.2.1 Outcomes included (research question 3)

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

The data availability at outcome level for research question 3 and research question 2 was identical (Table 11 in Section 2.5.2.1).

2.6.2.2 Risk of bias (research question 3)

Table 21 shows the risk of bias for the relevant outcomes.

Table 21: Risk of bias at study and outcome level – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 3)

Study		Outcomes														
	Study level	All-cause mortality	Remission (CDAI ≤ 2.8)	Low disease activity (DAS28-4 ESR ≤ 3.2)	Tender joints	Swollen joints[a]	Pain (VAS)	Disease activity (VAS)	Fatigue (FACIT-Fatigue)	Physical functioning (HAQ-DI)	Sleep disturbances (MOS sleep scale)	Health-related quality of life (SF-36v2 acute)	SAEs	Discontinuation due to AEs	Infections[b]	Serious infections
ORAL STANDARD	N	-[c]	H[d]	H[d]	H[d]	H[d]	–[e]	–[e]	H[d]	H[d]	–[e]	H[d]	H[f]	N	H[f]	-[c]

a: Based on 28 joints.
b: Any AEs of the SOC "infections and infestations".
c: The company did not present data for the subpopulation.
d: Large proportion of values imputed (> 15%).
e: The available data were not usable, see Section of the full dossier assessment for reasons.
f: Unclear proportion of patients who were not completely observed.

AE: adverse event; CDAI: Clinical Disease Activity Index; DAS28: Disease-Activity-Score-28; ESR: erythrocyte sedimentation rate; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; H: high; HAQ-DI: Health Assessment Questionnaire-Disability Index; MOS: Medical Outcome Study; MTX: methotrexate; RCT: randomized controlled trial; SF-36v2: Short Form 36 – version 2 Health Survey; SAE: serious adverse event; SOC: System Organ Class, VAS: visual analogue scale; vs.: versus

The assessment of the risk of bias for research questions 2 and 3 was identical for all outcomes (see Section 2.5.2.2). For research questions 2 and 3, the assessments of the risk of bias at outcome level deviated from those of the company in the same way. The risk of bias for the outcome "discontinuation due to AEs" was rated as low. The risk of bias was rated as high for all further outcomes for which analyses were available for the relevant subpopulation.

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

2.6.2.3 Results (research question 3)

Table 22 and Table 23 summarize the results of the comparison of tofacitinib + MTX with adalimumab + MTX in patients with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with several cDMARDs (including MTX) and poor prognostic factors. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations.

Table 22: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 3)

Study Outcome category Outcome	Tofacitinib + MTX		Adalimumab + MTX		Tofacitinib + MTX vs. adalimumab + MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
ORAL STANDARD					
Mortality					
All-cause mortality	100	0 (0)	103	ND[b]	–
Morbidity – proportion of patients with improvement					
Remission (CDAI ≤ 2.8)[c]	100	14 (14.0)	103	14 (13.6)	1.03 [0.52; 2.05]; < 0.971
low disease activity DAS28-4 ESR ≤ 3.2[d]	91	17 (18.7)	91	24 (25.8)	0.72 [0.42; 1.25]; < 0.245
tender joints[e] (≤ 1)	100	27 (27.0)	103	33 (32.0)	0.84 [0.55; 1.29]; < 0.532
swollen joints[e] (≤ 1)	100	42 (42.0)	103	37 (35.9)	1.17 [0.83; 1.65]; < 0.529
Fatigue (FACIT-Fatigue)[f]	100	53 (53.0)	103	51 (49.5)	1.07 [0.82; 1.40]; < 0.682
Physical functioning (HAQ-DI)[g]	100	56 (56.0)	103	65 (63.1)	0.89 [0.71; 1.11]; < 0.326
Side effects					
AEs (supplementary information)	103	75 (72.8)	104	78 (75.0)	–
SAEs	103	17 (16.5)	104	13 (12.5)	1.32 [0.68; 2.58]; 0.531
Discontinuation due to AEs	103	13 (12.6)	104	16 (15.4)	0.82 [0.42; 1.62]; < 0.682
Infections[h]	103	37 (35.9)	104	40 (38.5)	0.93 [0.66; 1.33]; < 0.769
serious infections	No usable data				

a: Institute's calculation, unconditional exact test (CSZ method according to [7].
b: At most 1 patient in the adalimumab arm, it is unclear whether death occurred in this subpopulation.
c: Further remission criteria, n (%):
- SDAI ≤ 3,3: tofacitinib + MTX (N = 100): 14 (14.0) vs. adalimumab + MTX (N = 103): 17 (16.5)
- American-College-of-Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria (Boolean definition): tofacitinib + MTX (N = 100): 11 (11.0) vs. adalimumab + MTX (N = 103): 10 (9.7)

d: Results DAS28-4 CRP ≤ 3.2, n (%): tofacitinib + MTX (N = 100): 44 (44.0) vs. adalimumab + MTX (N = 103): 44 (42.7).
e: Based on 28 joints.
f: Patients with improvement by ≥ 4 points.
g: Patients with improvement by ≥ 0.22 points.
h: Any AE of the SOC "infections and infestations".

ACR: American College of Rheumatology; AE: adverse event; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: Disease-Activity-Score-28; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; CI: confidence interval; MTX: methotrexate; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; SDAI: Simplified Disease Activity Index; SAE: serious adverse event; vs.: versus

Table 23: Results (morbidity and health-related quality of life, continuous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 3)

Study Outcome category Outcome	Tofacitinib + MTX			Adalimumab + MTX			Tofacitinib + MTX vs. adalimumab + MTX
	N[a]	Values at start of study mean (SD)	Change at end of study mean[b] (SD)	N[a]	Values at start of study mean (SD)	Change at end of study mean[b] (SD)	MD [95% CI]; p-value[c]
ORAL STANDARD							
Morbidity							
Pain (VAS)	No usable data						
Disease activity (VAS)	No usable data						
Sleep disturbances (MOS sleep scale)	No usable data						
Health-related quality of life							
SF-36v2 acute[d]							
Physical sum score	100	33.5 (7.91)	8.1 (8.02)	103	33.2 (6.78)	7.6 (7.65)	0.63 [−1.45; 2.71]; 0.551
Mental sum score	100	40.2 (10.29)	4.7 (10.76)	103	41.0 (11.96)	4.2 (10.66)	0.20 [−2.35; 2.75]; 0.878

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Based on patients for whom values were available at month 12, N = 79 (77) vs. N = 82 (82).
c: From an MMRM (fixed effects: treatment, time point of the study, treatment × time point of the study, region, baseline value; random effect: Patient).
d: Higher values indicate improvement.
CI: confidence interval; MMRM: mixed-effects model repeated measures; MOS: Medical Outcome Study; MTX: methotrexate; MW: mean value; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SF-36v2: Short Form 36 –version 2 Health Survey; VAS: visual analogue scale; vs.: versus

One relevant study was available for the assessment of the added benefit of tofacitinib. In view of the low risk of bias, at most an indication of an added benefit can be derived for the outcome “discontinuation due to AEs”. For all other outcomes, at most hints of an added benefit can be derived due to the high risk of bias (see Section 2.6.2.2, and Section 2.9.2.4.2 of the full dossier assessment).

This partly deviates from the assessment of the company, which rated the risk of bias as low for most outcomes and therefore considered the derivation of an indication of an added benefit for all outcomes to be justified.

Mortality

All-cause mortality

There were no usable data for the outcome "all-cause mortality" for the subpopulation. Only 1 patient of the total study population died during the observation period in the relevant study arms, namely in the adalimumab arm. This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company insofar as the company did not use the outcome "all-cause mortality" in its assessment.

Morbidity

Remission

No statistically significant difference between the treatment groups was shown for the outcome "remission" (Clinical Disease Activity Index [CDAI] ≤ 2.8). This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This corresponds to the company's assessment which also derived no added benefit for the outcome "remission" (operationalized using several remission criteria, e.g., DAS28-4 < 2.8; CDAI ≤ 2.8; SDAI ≤ 3.3 and the Boolean definition according to ACR/EULAR).

Low disease activity

No statistically significant difference between the treatment groups was shown for the outcome "low disease activity" (DAS28-4 ESR ≤ 3.2). This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company, which also derived no added benefit for the outcome "low disease activity" (operationalized using the achievement of several criteria, e.g., DAS28-4 ESR ≤ 3.2; DAS28-4 CRP ≤ 3.2; CDAI ≤ 10, SDAI ≤ 11).

Tender joints and swollen joints

No statistically significant difference between the treatment groups was shown for the outcomes "tender joints" and "swollen joints" for the number of responders (≤ 1 tender / swollen joint). This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for these outcomes; an added benefit is therefore not proven.

This concurs with the assessment of the company, which also claimed no added benefit for the outcomes "tender joints" and "swollen joints".

Pain (VAS)

The company presented no usable data for the outcome "pain (VAS)". This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

In addition, the company used analyses of the proportions of patients with a VAS improvement by ≥ 10 mm in its assessment. This response criterion was considered to be unvalidated (see Section 2.9.2.4.3 of the full dossier assessment). On the basis of the responder analyses, the company also derived no added benefit.

Disease activity (VAS)

The company presented no usable data for the outcome "disease activity" (VAS). This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

In addition, the company used analyses of the proportions of patients with a VAS improvement by ≥ 10 mm in its assessment. This response criterion was considered to be unvalidated (see Section 2.9.2.4.3 of the full dossier assessment). On the basis of the responder analyses, the company also derived no added benefit.

Fatigue (FACIT-Fatigue)

No statistically significant difference between the treatment groups was shown for the number of responders (improvement ≥ 4) for the outcome "Fatigue" (FACIT-Fatigue). This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company, which claimed no added benefit for the outcome "Fatigue (FACIT-Fatigue)".

Physical functioning (HAQ-DI)

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

This concurs with the assessment of the company, which also claimed no added benefit for the outcome "physical functioning" (improvement in HAQ-DI by ≥ 0.22 points). The company considered analyses on the different response criteria of an improvement by ≥ 0.22, ≥ 0.3 as well as ≥ 0.5.

Sleep disturbances (MOS sleep scale)

There were no usable data for the outcome "sleep disturbances" (MOS sleep scale) (see Section 2.9.2.4.3 of the full dossier assessment). This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

The company also derived no added benefit for the outcome "sleep disturbances (MOS sleep scale)".

Health-related quality of life

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

For the physical and the mental component summary of the SF-36v2 acute, no statistically significant difference between the treatment groups was shown for the mean change. This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for these outcomes; an added benefit is therefore not proven.

This deviates from the company's assessment insofar as the company considered responder analyses based on a minimally important difference (MID) ≥ 2.5 when deriving an added benefit. This response criterion was considered to be unvalidated (see Section 2.9.2.4.3 of the full dossier assessment). However, the company also claimed no added benefit on the basis of the responder analyses.

Side effects

SAEs, discontinuation due to AEs and infections

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

This corresponds to the company's assessment.

Serious infections

There were no usable data on the outcome "serious infections" for the relevant subpopulation, because the company had not analysed this prespecified outcome for the subpopulation (see Section 2.9.2.4.3 of the full dossier assessment). Table 31 and Table 32 in Appendix A show information on SAEs of the SOC "infections and infestations" as well as a list of the SAEs for the total population of the ORAL STANDARD study. These analyses show that a relevant proportion of the SAEs were infections.

Given the missing data for this outcome, there was altogether no hint of greater or lesser harm from tofacitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven.

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

2.6.2.4 Subgroups and other effect modifiers (research question 3)

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

For research question 3, there were no subgroup results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) (see Section 2.9.2.4,.of the full dossier assessment).

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

The probability and extent of added benefit for patients with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with several cDMARDs (including MTX) were derived on outcome level. The different outcome categories and the effect sizes are taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [8].

This procedure for deriving an overall conclusion on the added benefit based on the aggregation of the conclusions deduced at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

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

The data presented in Section 2.6.2 resulted in no statistically significant and relevant effects of tofacitinib + MTX in comparison with adalimumab + MTX in patients with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with several cDMARDs (including MTX). The extent of the respective added benefit at outcome level was estimated from these results (see Table 24).

Table 24: Extent of added benefit at outcome level: tofacitinib + MTX vs. adalimumab + MTX (research question 3)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Tofacitinib + MTX vs. adalimumab + MTX** **Proportion of patients with event or change** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	Proportion: 0% vs. no data[c]	–
Morbidity		
Remission (CDAI ≤ 2.8)[d]	Proportion: 14.0% vs. 13.6% RR: 1.03 [0.52; 2.05]; p = 0.971	Lesser benefit/added benefit not proven
Low disease activity (DAS28-4 ESR ≤ 3.2)[e]	Proportion: 18.7% vs. 25.8% RR: 0.72 [0.42; 1.25]; p = 0.245	Lesser benefit/added benefit not proven
Tender joints (≤ 1)	Proportion: 27.0% vs. 32.0% RR: 0.84 [0.55; 1.29]; p = 0.532	Lesser benefit/added benefit not proven
Swollen joints (≤ 1)	Proportion: 42.0% vs. 35.9% RR: 1.17 [0.83; 1.65]; p = 0.529	Lesser benefit/added benefit not proven
Pain (VAS)	No usable data[f]	Lesser benefit/added benefit not proven
Disease activity (VAS)	No usable data[f]	Lesser benefit/added benefit not proven
Fatigue (FACIT-Fatigue)[g]	Proportion: 53.0% vs. 49.5% RR: 1.07 [0.82; 1.40]; p = 0.682	Lesser benefit/added benefit not proven
physical functioning (HAQ-DI)[h]	Proportion: 56.0% vs. 63.1% RR: 0.89 [0.71; 1.11]; p = 0.326	Lesser benefit/added benefit not proven
Sleep disturbances (MOS sleep scale)	No usable data[f]	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36v2 acute		
Physical sum score	Mean change between start of the study and month 12: 8.1 vs. 7.6 MD: 0.63 [−1.45; 2.71]; p = 0.551	Lesser benefit/added benefit not proven
Mental sum score	Mean change between start of the study and month 12: 4.7 vs. 4.2 MD: 0.20 [−2.35; 2.75]; p = 0.878	Lesser benefit/added benefit not proven

(continued)

Table 24: Extent of added benefit at outcome level: tofacitinib + MTX vs. adalimumab + MTX (research question 3) (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Tofacitinib + MTX vs. adalimumab + MTX** **Proportion of patients with event or change** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
SAEs	Proportion: 16% vs. 12.5% RR: 1.32 [0.68; 2.58]; p = 0.531	Greater/lesser harm not proven
Discontinuation due to AEs	Proportion: 12.6% vs. 15.4% RR: 0.82 [0.42; 1.62]; p = 0.682	Greater/lesser harm not proven
Infections	Proportion: 35.9% vs. 38.5% RR: 0.93 [0.66; 1.33]; p = 0.769	Greater/lesser harm not proven
serious infections	No usable data[i]	Greater/lesser harm not proven

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: At most 1 patient in the adalimumab arm.
d: The results of the other remission criteria SDAI ≤ 3.3 and according to ACR/EULAR are consistent.
e: The relevant results for the operationalization as DAS28-4 CRP ≤ 3.2 are consistent.
f: No usable data for the relevant subpopulation available; see Section 2.9.2.4.3 of the full dossier assessment for reasons.
g: Patients with improvement by ≥ 4 points.
h: Patients with improvement by ≥ 0.22 points.
i: The company presented no analyses for the relevant subpopulation for this outcome.

ACR American College of Rheumatology; AE: adverse event; CDAI: Clinical Disease Activity Index; DAS28: Disease-Activity-Score-28; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; CI: confidence interval; MD: mean difference; MOS: Medical Outcome Study; MTX: methotrexate; RR: relative risk; SDAI: Simplified Disease Activity Index; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus.

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

Table 25 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 25: Positive and negative effects from the assessment of tofacitinib + MTX in comparison with adalimumab + MTX (research question 3)

Positive effects	**Negative effects**
–	–
MTX: methotrexate	

Overall, neither positive nor negative effects were found. This resulted in no hint of an added benefit of tofacitinib in comparison with the ACT for patients with moderate to severe active

rheumatoid arthritis who have responded inadequately to prior treatment with several cDMARDs (including MTX). An added benefit is therefore not proven.

This concurs with the approach of the company, which also derived no added benefit on the basis of the subpopulations for patients of research question 3.

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

2.6.4 List of included studies (research question 3)

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

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

2.7.1 Results on added benefit (research question 4)

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

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

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

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

2.7.3 List of included studies (research question 4)

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

2.8 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of tofacitinib in comparison with the ACT is summarized in Table 26.

Table 26: Tofacitinib – probability and extent of added benefit

Research question[a]	**Therapeutic indication**	**ACT**[b]	**Probability and extent of added benefit**
1	Patients without poor prognostic factors[c] who have responded inadequately to prior treatment with one conventional DMARD	Alternative conventional DMARDs (e.g. MTX, leflunomide), if suitable, as monotherapy or combination therapy	Added benefit not proven
2	Patients with poor prognostic factors[c] who have responded inadequately to prior treatment with 1 conventional DMARD[d].	Biologic disease-modifying antirheumatic drug (bDMARD) in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance	*Patients ≤ 65 years* Hint of lesser benefit *Patients > 65 years* Added benefit not proven
3	Patients who have responded inadequately to prior treatment with several DMARDs (conventional DMARDs, including MTX)	Biologic disease-modifying antirheumatic drug (bDMARD) in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance	Added benefit not proven
4	Patients who have responded inadequately to prior treatment with 1 or several bDMARDs	Switching of bDMARD treatment (adalimumab or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab); in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance; or in patients with severe rheumatoid arthritis, rituximab under consideration of the approval depending on prior therapy	Added benefit not proven

a: Research questions 1, 2, 3 and 4 correspond to the respective subpopulations b, c, d and e of the company.
b: 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**.
c: Poor prognostic factors, for instance, detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.
d: According to the SPC, tofacitinib is also approved for patients who have not tolerated prior treatment with a DMARD [3]. The relevant subpopulation of the included study for the assessment of the added benefit (only patients who have shown inadequate response to MTX) therefore does not completely cover the therapeutic indication. It remains unclear whether the observed effects can be transferred to patients who have not tolerated prior treatment with a DMARD.

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

Research questions 1 and 4

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

Research question 2

Patients ≤ 65 years

There is a hint of lesser benefit of tofacitinib in comparison with the ACT adalimumab for patients ≤ 65 years with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with 1 cDMARD and with poor prognostic factors (research question 2).

Patients > 65 years

The added benefit of tofacitinib in comparison with the ACT is not proven for patients > 65 years with moderate to severe active rheumatoid arthritis with inadequate response to prior treatment with 1 cDMARD and with poor prognostic factors (research question 2).

This deviates from the approach of the company, which overall derived no added benefit for patients of research question 2.

Research question 3:

An added benefit of tofacitinib in comparison with the ACT is not proven for patients with moderate to severe active rheumatoid arthritis who have responded inadequately to prior treatment with several cDMARDs (including MTX) (research question 3). This corresponds to the company's assessment.

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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