IQWiG Reports – Commission No. A21-115

Tofacitinib (rheumatoid arthritis) –

Benefit assessment according to §35a Social Code Book V[1] (new scientific findings, assessment after expiry of the decision)

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Tofacinib (rheumatoide Arthritis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 November 2021). 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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Medical and scientific advice

No advisor on medical and scientific questions was available for the present dossier assessment.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent for participating in the written exchange about how he experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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Table of contents

Page

List of tables ..... **iv**
List of abbreviations ..... **v**
2 Benefit assessment **1**
2.1 Executive summary of the benefit assessment **1**
2.2 Research question **7**
2.3 Information retrieval and study pool **8**
2.4 Results on added benefit **15**
2.5 Probability and extent of added benefit **16**
References for English extract **19**

List of tables[2]

Page

Table 2: Research questions on the benefit assessment of tofacitinib 2
Table 3: Tofacitinib – probability and extent of added benefit 6
Table 4: Research questions on the benefit assessment of tofacitinib 8
Table 5: Evidence provided by the company – RCT, direct comparison: tofacitinib + MTX vs. TNFi + MTX 10
Table 6: Tofacitinib – probability and extent of added benefit 17

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

List of abbreviations

Abbreviation	Meaning
ACR	American-College-of-Rheumatology
ACR50	50% improvement in ACR
ACT	appropriate comparator therapy
AE	adverse event
bDMARD	biologic DMARD
CHD	coronary heart disease
DMARD	disease-modifying antirheumatic drug
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HDL	high-density lipoprotein
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MACE	major adverse cardiac events
MTX	methotrexate
NMSC	non-melanoma skin cancer
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
tDMARD	targeted synthetic DMARD
TNFi	tumour necrosis factor inhibitors

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 pharmaceutical company (hereinafter referred to as "the company") submitted a first dossier for the early benefit assessment of the drug to be assessed on 26 April 2017. In this procedure, the G-BA limited its decision. Accordingly, the company submitted a new dossier for the early benefit assessment on 30 April 2018. On 18 March 2021, the G-BA requested a new benefit assessment because of new scientific findings. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as “the company”). The dossier was sent to IQWiG on 31 August 2021.

Research question

The aim of the present report is the assessment of the added benefit of tofacitinib in combination with methotrexate (MTX) or as monotherapy if MTX is not tolerated or treatment with MTX is unsuitable, in comparison with the appropriate comparator therapy (ACT) in adult patients with moderate to severe active rheumatoid arthritis who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs).

The research questions shown in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions on the benefit assessment of tofacitinib

Research question	Therapeutic indication	ACT[a]
Adults with moderate to severe active rheumatoid arthritis		
1	Patients without poor prognostic factors[b] who have responded inadequately to, or who have not tolerated prior treatment with one disease-modifying antirheumatic drug (csDMARDs[c], including methotrexate [MTX])	Alternative csDMARDs[c], if suitable (e.g. MTX, leflunomide, sulfasalazine), as monotherapy or combination therapy
2	Patients for whom a first therapy with bDMARDs or tsDMARDs is indicated[d]	bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or updacatinib) in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability
3	Patients who have responded inadequately to or did not tolerate prior treatment with one or more bDMARDs and/or tsDMARDs	Switching of bDMARDs or tsDMARDs therapy (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or upadactinib in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability; or, in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on the pretreatment

a. Presentation of the respective ACT specified by the G-BA.
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. In the G-BA's specification of the ACT, csDMARDs are referred to as “classical DMARDs”. The present benefit assessment uses the term “csDMARDs”.
d. This comprises both patients with poor prognostic factors who have responded inadequately to or have not tolerated prior treatment with one csDMARD (including MTX), and patients who have responded inadequately to or have not tolerated prior treatment with several csDMARDs (including MTX).

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

The company followed the G-BA's specification of the ACT.

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.

Study pool

The company considered the studies ORAL STANDARD, ORAL STRATEGY and ORAL SURVEILLANCE, which it all assigned to research question 2. The company presented no data for research questions 1 and 3. The studies ORAL STANDARD and ORAL STRATEGY are already known from benefit assessments A17-18 and A18-28 and were used for the benefit assessment. The company only used the studies ORAL STANDARD and ORAL STRATEGY for the assessment of the added benefit of tofacitinib. The company classified the ORAL SURVEILLANCE study as irrelevant.

Concurring with the company, the ORAL SURVEILLANCE study is considered to be irrelevant for the present benefit assessment. The studies ORAL STANDARD and ORAL STRATEGY are relevant, however, suitable analyses are not available. This is due to the fact that the approval of tofacitinib has changed in comparison with the previous assessments A17-18 and A18-28 and the company presented no analyses for the relevant population. Both aspects are explained below.

Study ORAL SURVEILLANCE is not relevant

ORAL SURVEILLANCE is an RCT which compared 2 different dosages of tofacitinib (5 mg or 10 mg twice daily [bid]) in combination with MTX versus the tumour necrosis factor inhibitors (TNFi) adalimumab or etanercept each in combination with MTX in adults with moderate to severe active rheumatoid arthritis and inadequate response to MTX. The study was prompted by requests of the Food and Drug Administration (FDA) to investigate the post-approval safety profile of tofacitinib. The study only included patients ≥ 50 years with at least 1 cardiovascular risk factor.

Coprimary outcomes of the ORAL SURVEILLANCE study were major adverse cardiac events (MACE)" and malignancies (except for non-melanoma skin cancer [NMSC]). Secondary outcomes were outcomes of the categories "morbidity", "health-related quality of life" and "adverse events (AEs)".

The study did not meet the non-inferiority criterion for the primary comparison of the combined tofacitinib arms with the TNFi arm regarding MACE and malignancies (excluding NMSC). As a result, the approval of tofacitinib was restricted so that patients > 65 years of age, patients who are smokers or former smokers and patients with other cardiovascular risk factors or other risk factors for malignancies (e.g. current or past malignancy, excluding a successfully treated NMSC) shall only be treated with tofacitinib if no suitable treatment alternatives are available.

As the ORAL SURVEILLANCE study only included patients with at least 1 cardiovascular risk factor, this treatment restriction applied to all patients of the study. The majority of the included patient population were patients for whom a first therapy with biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) was indicated. In principle, all drugs that the G-BA specified as ACT for research question 2 are suitable treatment alternatives for this patient population. This also includes the drugs adalimumab and etanercept (which were

administered in the comparator arm of the ORAL SURVEILLANCE study), for which there is no restriction of the approval analogous to tofacitinib and which thus represent suitable treatment alternatives as examples. For patients in the ORAL SURVEILLANCE study, tofacitinib thus presented no adequate treatment according to the current approval. Therefore, the ORAL SURVEILLANCE study is not suitable for the assessment of the added benefit of tofacitinib.

Studies ORAL STANDARD and ORAL STRATEGY

The studies ORAL STANDARD and ORAL STRATEGY were already known from the first assessment of tofacitinib in the present therapeutic indication (dossier assessment A17-18) and the reassessment after expiry of the decision (dossier assessment A18-28) and were used for the assessment.

Both studies are RCTs on the comparison of tofacitinib + MTX versus adalimumab + MTX that included adult patients with active rheumatoid arthritis and inadequate response to MTX.

Populations presented by the company are not suitable for the assessment of the added benefit of tofacitinib

The company used the two total populations of the studies ORAL STANDARD and ORAL STRATEGY for the assessment of the added benefit of tofacitinib. Moreover, the company presented supplementary analyses on the two studies for the patient population ≥ 50 years of age with at least 1 cardiovascular risk factor. The company provided no concrete information on the definition of the cardiovascular risk factors. It is assumed that the definition corresponds to the inclusion criteria of the ORAL SURVEILLANCE study. According to the information on the characteristics of this patient population provided by the company in Module 4 A, this subpopulation comprised a total of 157 (39.5%) patients from the ORAL STANDARD study and 254 (33.3%) patients from ORAL STRATEGY. Consequently, the overall population of both studies includes a relevant proportion of patients for whom treatment with tofacitinib is not indicated according to the current approval because suitable treatment alternatives (according to the ACT) are available (see the explanations on the ORAL SURVEILLANCE study).

In its dossier, the company formed no subpopulations of the studies ORAL STANDARD and ORAL STRATEGY that corresponded to the current approval. Separate subgroup analyses for the combination of the characteristics “cardiovascular risk factors” and “age” (≥ 1 cardiovascular risk factor and ≥ 50 years of age [subpopulation “CV subset”] vs. other [subpopulation “Other”] can be found in Appendix 4 G of Module 4 A of the full benefit assessment. The subpopulation CV subset corresponds to the patient population cited in the previous section, which the company presented as supplementary information. The subpopulation Other comprised all other patients of the total populations of the studies ORAL STANDARD and ORAL STRATEGY. However, it is also true for the respective subpopulations Other that they still include a relevant proportion of patients who, according to

the current approval, should only be treated with tofacitinib if no suitable treatment alternatives are available.

Hence, neither the analyses on the total population nor those on the subpopulation Other are suitable for the assessment of the added benefit of tofacitinib in the present benefit assessment.

Results on added benefit

For the assessment of the added benefit of tofacitinib versus the ACT in adult patients with moderate to severe active rheumatoid arthritis who have responded inadequately to or who are intolerant to one or more DMARDs, no data are available for research questions 1 and 3 and no suitable analyses are available for research question 2. In each case, this resulted in no hint of an added benefit of tofacitinib in comparison with the ACT for all 3 research questions, an added benefit is therefore not proven.

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

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

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

Table 3: Tofacitinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with moderate to severe active rheumatoid arthritis			
1	Patients without poor prognostic factors[b] who have responded inadequately to, or who have not tolerated prior treatment with one disease-modifying antirheumatic drug (csDMARDs[c], including methotrexate [MTX])	Alternative csDMARDs[c], if suitable (e.g. MTX, leflunomide, sulfasalazine), as monotherapy or combination therapy	Added benefit not proven
2	Patients for whom a first therapy with bDMARDs or tsDMARDs is indicated[d]	bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or updacatinib) in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability	Added benefit not proven
3	Patients who have responded inadequately to or did not tolerate prior treatment with one or more bDMARDs and/or tsDMARDs	Switching of bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or upadactinib in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability; or, in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on the pretreatment	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
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. In the G-BA's specification of the ACT, csDMARDs are referred to as “classical DMARDs”. The present benefit assessment uses the term “csDMARDs”.
d. This comprises both patients with poor prognostic factors who have responded inadequately to or have not tolerated prior treatment with one csDMARD (including MTX), and patients who have responded inadequately to or have not tolerated prior treatment with several csDMARDs (including MTX).

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

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of tofacitinib in combination with MTX or as monotherapy if MTX is not tolerated or treatment with MTX is unsuitable, in comparison with the ACT in adult patients with moderate to severe active rheumatoid arthritis who have responded inadequately to, or who are intolerant to one or more DMARDs.

The research questions shown in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions on the benefit assessment of tofacitinib

Research question	Therapeutic indication	ACT[a]
Adults with moderate to severe active rheumatoid arthritis		
1	Patients without poor prognostic factors[b] who have responded inadequately to, or who have not tolerated prior treatment with one disease-modifying antirheumatic drug (csDMARDs[c], including methotrexate [MTX])	Alternative csDMARDs[c], if suitable (e.g. MTX, leflunomide, sulfasalazine), as monotherapy or combination therapy
2	Patients for whom a first therapy with bDMARDs or tsDMARDs is indicated[d]	bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or updacatinib) in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability
3	Patients who have responded inadequately to or did not tolerate prior treatment with one or more bDMARDs and/or tsDMARDs	Switching of bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or upadactinib in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability; or, in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on the pretreatment

a. Presentation of the respective ACT specified by the G-BA.
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. In the G-BA's specification of the ACT, csDMARDs are referred to as “classical DMARDs”. The present benefit assessment uses the term “csDMARDs”.
d. This comprises both patients with poor prognostic factors who have responded inadequately to or have not tolerated prior treatment with one csDMARD (including MTX), and patients who have responded inadequately to or have not tolerated prior treatment with several csDMARDs (including MTX).

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

The company followed the G-BA's specification of the ACT.

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: 28 July 2021)
- bibliographical literature search on tofacitinib (last search on 28 June 2021)
- search in trial registries/trial results databases for studies on tofacitinib (last search on 28 June 2021)
- search on the G-BA website for tofacitinib (last search on 05 July 2021)

To check the completeness of the study pool:

- search in trial registries for studies on tofacitinib (last search on 15 September 2021); for search strategies, see Appendix A of the full dossier assessment

The company identified the studies ORAL STANDARD, ORAL STRATEGY, ORAL SURVEILLANCE and Xeljanz2014. The company stated that it would not consider the Xeljanz2014 study further, as no results on patient-relevant outcomes were available in an operationalization that was accepted in the context of the benefit assessment.

No additional potentially relevant studies were identified from the check of the completeness of the study pool. For the Xeljanz2014 study (with 50 patients), it is not possible to infer from the publication Nakamura et al. [3] to what extent patients were included in this study for the present research questions, as only limited information is available on the characteristics of the study population. Therefore, the data from the Nakamura et al. publication are not usable within the framework of the present benefit assessment. For information on the relevance of the studies ORAL STANDARD, ORAL STRATEGY and ORAL SURVEILLANCE for the present benefit assessment see the sections below.

Evidence provided by the company

Table 5: Evidence provided by the company – RCT, direct comparison: tofacitinib + MTX vs. TNFi + MTX

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
A3921064 (ORAL STANDARD[d])	Yes	Yes	No	Yes [4]	Yes [5,6]	Yes [7-15]
A3921187 (ORAL STRATEGY[d])	No	Yes	No	Yes [16]	Yes [17-19]	Yes [14,15,20-22]
A3921133 (ORAL SURVEILLANCE[d])	Yes	Yes	No	Yes [23]	Yes [24-26]	Yes [14,15]

a. Study for which the company was the sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to with this abbreviated form.

G-BA: Federal Joint Committee; MTX: methotrexate; RCT: randomized controlled trial; TNFi: tumour necrosis factor inhibitor

The company considered the studies ORAL STANDARD, ORAL STRATEGY and ORAL SURVEILLANCE (see Table 5), which it all assigned to research question 2 (referred to by the company as "subpopulation b"). The company presented no data for research questions 1 and 3. The studies ORAL STANDARD and ORAL STRATEGY were already known from the benefit assessments A17-18 [27] and A18-28 [28] and were used for the assessment.

The company only used the studies ORAL STANDARD and ORAL STRATEGY for the assessment of the added benefit of tofacitinib. The company classified the ORAL SURVEILLANCE study as irrelevant and therefore only presented the results as supplementary information in Module 4 A.

Concurring with the company, the ORAL SURVEILLANCE study is considered to be irrelevant for the present benefit assessment. The studies ORAL STANDARD and ORAL STRATEGY are relevant, however, suitable analyses are not available. This is due to the fact that the approval of tofacitinib has changed in comparison with the previous assessments A17-18 and A18-28 and the company presented no analyses for the relevant population. Both aspects are explained below.

Study ORAL SURVEILLANCE

ORAL SURVEILLANCE is a randomized, open-label and multicentre study which compared 2 different dosages of tofacitinib (5 mg or 10 mg bid) in combination with MTX (hereinafter referred to as tofacitinib + MTX) versus the TNFi adalimumab or etanercept, each in combination with MTX (hereinafter referred to as TNFi + MTX).

The study was prompted by requests of the FDA to investigate the post-approval safety profile of tofacitinib. The study included adult patients ≥ 50 years of age with moderate to severe active rheumatoid arthritis who had an inadequate response to previous treatment with MTX. Moreover, the patients had to have at least 1 of the following cardiovascular risk factors:

- Current smoking
- Hypertension
- High-density lipoprotein (HDL) < 40 mg/dL
- Diabetes mellitus
- Family history of coronary heart disease (CHD) (documented clinical CHD or sudden death of a first-degree male relative < 55 years or first-degree female relative < 65 years)
- Rheumatoid arthritis-associated extraarticular diseases (e.g. Nodules, Sjögren's syndrome, anaemia associated with chronic disease, pulmonary manifestations)
- History of CHD (including history of revascularization procedures, coronary bypass transplantation, myocardial infarction, cardiac arrest, unstable angina pectoris and acute coronary syndrome)

ORAL SURVEILLANCE included a total of 4372 patients who were randomly assigned to either treatment with 5 mg tofacitinib + MTX bid (N = 1457), 10 mg tofacitinib + MTX bid (N = 1457) or TNFi + MTX (N = 1458) in a 1:1:1 ratio. Only the study arms tofacitinib 5 mg bid + MTX as well as TNFi + MTX were considered for the present assessment, therefore, the subsequent description only refers to these study arms.

In the ORAL SURVEILLANCE study, treatment with tofacitinib and adalimumab or etanercept was largely performed in compliance with the dosage instructions of the respective SPC [29-31]. All patients received concomitant MTX treatment.

Treatment was to be continued until ≥ 1500 patients had been observed for ≥ 3 years and at least 103 MACEs and 138 malignancies (excluding NMSC) had occurred. The final data cut-off took place on 22 July 2020.

Coprimary outcomes of the ORAL SURVEILLANCE study were MACE and malignancies (except for NMSC). Secondary outcomes were outcomes of the categories "morbidity", "health-related quality of life" and "AEs".

Within the framework of the present benefit assessment, data on the ORAL SURVEILLANCE study are presented as supplementary information in Appendix B of the full dossier assessment.

ORAL SURVEILLANCE study not relevant for the benefit assessment

In the ORAL SURVEILLANCE study, the non-inferiority criterion for the primary comparison of the combined tofacitinib arms with the TNFi arm was not met because the upper limit of the 95% CI for the HR exceeded the prespecified non-inferiority criterion of 1.8 for MACE and malignancies (except for NMSC) (MACE: HR: 1.33; 95% CI: [0.91; 1.94]; malignancies other than NMSC: HR: 1.48; 95% CI: [1.04; 2.09]). As a result, the approval of tofacitinib was restricted so that patients > 65 years of age, patients who are smokers or former smokers and patients with other cardiovascular risk factors or other risk factors for malignancies (e.g. current or past malignancy, excluding a successfully treated NMSC) shall only be treated with tofacitinib if no suitable treatment alternatives are available [29,32].

The ORAL SURVEILLANCE study only included patients who had at least 1 cardiovascular risk factor. According to the current approval, treatment with tofacitinib would only be an option for this patient population if no suitable treatment alternatives were available. Overall, the majority of patients included in the ORAL SURVEILLANCE study were patients for whom a first therapy with bDMARDs or tsDMARDs was indicated (except for approx. 10% who had been pretreated with bDMARDs or tsDMARDs, see Table 12 in Appendix B.3 of the full dossier assessment). In principle, however, all or the majority of the drugs that the G-BA had defined as ACT for research question 2 (see Table 4) were suitable treatment alternatives for all included patients, regardless of prior treatment. This also includes the drugs adalimumab and etanercept (which were administered in the comparator arm of the ORAL SURVEILLANCE study), for which there is no restriction of the approval analogous to tofacitinib [30,31] and which thus represent suitable treatment alternatives as examples. For patients in the ORAL SURVEILLANCE study, tofacitinib thus presented no adequate treatment according to the current approval. Therefore, the ORAL SURVEILLANCE study is not suitable for the assessment of the added benefit of tofacitinib.

This assessment concurs with the assessment of the company, which also did not use the study for the derivation of the added benefit. The company stated that it would present the ORAL SURVEILLANCE study as supplementary information in Module 4 A for reasons of transparency.

Studies ORAL STANDARD and ORAL STRATEGY

The studies ORAL STANDARD and ORAL STRATEGY are relevant for the present benefit assessment. Both studies were already known from the first assessment of tofacitinib in the present therapeutic indication (dossier assessment A17-18 [27] and the reassessment after expiry of the decision (dossier assessment A18-28 [28]) and were used for the assessment.

The studies ORAL STANDARD and ORAL STRATEGY were randomized, double-blind and multicentre parallel-group studies (see Appendix C of the full dossier assessment, further

information on the characteristics of the interventions and the study population can be found in the previous dossier assessments). Each of the studies included adult patients with active rheumatoid arthritis and inadequate response to MTX.

The ORAL STANDARD study included a total of 717 patients who were randomly assigned to the arms tofacitinib 5 mg bid + MTX (N = 204), tofacitinib 10 mg bid + MTX (N = 201), placebo + MTX (2 placebo arms: N = 56 and N = 52) and adalimumab + MTX (N = 204) in a 4:4:1:1:4 ratio.

ORAL STRATEGY included a total of 1152 patients who were randomly assigned to the arms 5 mg tofacitinib bid (N = 386), 5 mg tofacitinib bid + MTX (N = 378) and adalimumab + MTX (N = 388) in a 1:1:1 ratio. For the present assessment, the study arms tofacitinib 5 mg bid + MTX as well as adalimumab + MTX are relevant for both studies; therefore, the subsequent description only refers to these two study arms.

The planned treatment period was 12 months for both studies. Both studies are completed.

Primary outcomes of the ORAL STANDARD study were 20% improvement of the ACR criteria (ACR20) from the start of the study to month 6, as well as improvement of the Health Assessment Questionnaire-Disability Index (HAQ-DI) at month 3 and the Disease-Activity-Score-28-4-erythrocyte sedimentation rate (DAS28-4 ESR) < 2.6 at month 6. The patient-relevant outcomes on morbidity, health-related quality of life and AEs were also recorded.

Primary outcome of the ORAL STRATEGY study was the improvement in American-College-of-Rheumatology (ACR) criteria by 50% (ACR50) from the start of the study until month 6. Patient-relevant outcomes on morbidity, health-related quality of life and AEs were additionally recorded.

Total populations of the studies ORAL STANDARD and ORAL STRATEGY were not suitable for the assessment of the added benefit of tofacitinib

The company used the two total populations of the studies ORAL STANDARD and ORAL STRATEGY for the assessment of the added benefit of tofacitinib. In doing so, the company did not take into account the extent to which the two studies included patients for whom treatment with tofacitinib was not indicated according to the current approval, provided that suitable treatment alternatives were available (see section on the ORAL SURVEILLANCE study).

Moreover, the company presented supplementary analyses on the two studies for the patient population ≥ 50 years of age with at least 1 cardiovascular risk factor. The company provided no concrete information on the definition of the cardiovascular risk factors. It is assumed that the definition corresponds to the inclusion criteria of the ORAL SURVEILLANCE study. According to the information on the characteristics of this patient population provided by the company in Module 4 A, this subpopulation comprised a total of 157 (39.5%) patients from the

ORAL STANDARD study and 254 (33.3%) patients from ORAL STRATEGY. Consequently, the overall population of both studies includes a relevant proportion of patients for whom treatment with tofacitinib is not indicated according to the current approval because suitable treatment alternatives (according to the ACT) are available (see the explanations on the relevance of the ORAL SURVEILLANCE study). The analyses of the total populations of the two studies are thus not suitable for the assessment of the added benefit of tofacitinib.

No suitable subpopulations for the assessment of the added benefit of tofacitinib analysed

In its dossier, the company formed no subpopulations of the ORAL STANDARD and ORAL STRATEGY studies that correspond to the current approval. Separate subgroup analyses for the combination of the characteristics "cardiovascular risk factors" and "age" (≥ 1 cardiovascular risk factor and ≥ 50 years of age [subpopulation "CV subset"] vs. other [subpopulation "Other"]) can be found in Appendix 4 G of Module 4 A of the full benefit assessment. The subpopulation CV subset corresponds to the patient population cited in the previous section, which the company presented as supplementary information. The subpopulation Other comprised all other patients of the total populations of the studies ORAL STANDARD (N =240 [60.5%]) and ORAL STRATEGY (N = 508 [66.7%]). This subpopulation is also not suitable for the assessment of the added benefit, as it nevertheless includes a relevant number of patients who, according to the current approval, should only be treated with tofacitinib if no suitable treatment alternatives are available. This is explained below.

For the CV subset (patient population with ≥ 1 cardiovascular risk factor and ≥ 50 years of age), it is assumed that the company considered those cardiovascular risk factors that are reflected in the inclusion criteria of the ORAL SURVEILLANCE study. This includes current smoking, hypertension, HDL < 40 mg/dL, diabetes mellitus, family history of CHD, rheumatoid arthritis-associated extraarticular disease and history of CHD. However, the restrictions of the SPC go beyond these criteria. Also in former smokers, all patients > 65 years of age, all patients with cardiovascular risk factors regardless of age, as well as patients with other risk factors for malignancies (e.g. current or past malignancy, except for a successfully treated NMSC) tofacitinib should only be used if no suitable treatment alternatives are available [29].

The company did not provide any information for the subpopulation Other that would allow an assessment of the extent to which the patients mentioned were included. According to the exclusion criteria of the studies ORAL STANDARD and ORAL STRATEGY, patients with current or previous malignant disease other than adequately treated or removed non-metastatic basal cell or squamous cell carcinoma of the skin or cervical cancer in situ should not be included. For example, in can be inferred from the available information that the total populations of the ORAL STANDARD study included a total of at least 147 patients and the ORAL STRATEGY study included a total of at least 194 patients who were smokers or former smokers. The corresponding subgroup analyses for the CV subset subpopulation show that 75 of these 147 patients from the ORAL STANDARD study and 94 of these 194 patients from the ORAL STRATEGY study were included in this subpopulation. Thus, at least 72 (30%) patients

(ORAL STANDARD) and 100 (20%) patients (ORAL STRATEGY) who should not have been treated with tofacitinib according to the current approval were already included in the subpopulation Other due to this criterion (smokers or former smokers). The extent to which further patients cannot be assigned to the relevant subpopulation due to the mentioned restrictions of the SPC cannot be derived from the available information. However, the company would be able to form corresponding subpopulations.

Overall, it is not possible to estimate how many patients who were not to be treated with tofacitinib according to the approval were included in the subpopulation Other. This includes at least 30% of the patients in the ORAL STANDARD study and at least 20% of the patients in the ORAL STRATERGY study. Therefore, the subpopulation "Other" is not suitable for the assessment of the added benefit of tofacitinib.

Patients pretreated with bDMARDs do not correspond to research question 2

In addition, it was already pointed out in the context of benefit assessment A18-28 that the studies ORAL STANDARD and ORAL STRATEGY also included patients who had been pretreated with bDMARDs [28]. These patients are not part of research question 2 (patients for whom a first therapy with bDMARDs or tsDMARDs was indicated). In total, this concerns 34 (8.6%) patients in the total population of the ORAL STANDARD study and 64 (8.4%) patients in the total population of the ORAL STRATEGY study [28]. It is unclear how many of the patients were included in the subpopulation "Other".

Summary

The ORAL SURVEILLANCE study is not relevant for the present benefit assessment because the study population exclusively included patients with ≥ 1 cardiovascular risk factor. For such patients, treatment with tofacitinib was only indicated if no suitable treatment alternatives were available.

The two studies ORAL STANDARD and ORAL STRATEGY are relevant, however, suitable analyses are not available. The analyses on the total population and for the subpopulation Other presented in Module 4 A are not suitable for the assessment of the added benefit of tofacitinib, as both populations contain a relevant number of patients for whom tofacitinib is only indicated if no suitable treatment alternatives are available.

2.4 Results on added benefit

For the assessment of the added benefit of tofacitinib versus the ACT in adult patients with moderate to severe active rheumatoid arthritis who have responded inadequately to or who are intolerant to one or more DMARDs, no data are available for research questions 1 and 3 and no suitable analyses are available for research question 2. In each case, this resulted in no hint of an added benefit of tofacitinib in comparison with the ACT for all 3 research questions, an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

As no data are available for the assessment of the added benefit of tofacitinib versus the ACT in adult patients with moderate to severe active rheumatoid arthritis who have responded inadequately to or who are intolerant to one or more DMARDs no data are available for research questions 1 and 3 and no suitable analyses are available for research question 2, an added benefit of tofacitinib is not proven for these patients.

The result of the assessment of the added benefit of tofacitinib in comparison with the ACT is summarized in Table 6.

Table 6: Tofacitinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with moderate to severe active rheumatoid arthritis			
1	Patients without poor prognostic factors[b] who have responded inadequately to, or who have not tolerated prior treatment with one disease-modifying antirheumatic drug (csDMARDs[c], including methotrexate [MTX])	Alternative csDMARDs[c], if suitable (e.g. MTX, leflunomide, sulfasalazine), as monotherapy or combination therapy	Added benefit not proven
2	Patients for whom a first therapy with bDMARDs or tsDMARDs is indicated[d]	bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or updacatinib) in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability	Added benefit not proven
3	Patients who have responded inadequately to or did not tolerate prior treatment with one or more bDMARDs and/or tsDMARDs	Switching of bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or upadactinib in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability; or, in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on the pretreatment	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
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. In the G-BA's specification of the ACT, csDMARDs are referred to as “classical DMARDs”. The present benefit assessment uses the term “csDMARDs”.
d. This comprises both patients with poor prognostic factors who have responded inadequately to or have not tolerated prior treatment with one csDMARD (including MTX), and patients who have responded inadequately to or have not tolerated prior treatment with several csDMARDs (including MTX).

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

For all three research questions, the assessment described above corresponds to that of the company, which, for research question 2, used the study results for the total population of the studies ORAL STANDARD and ORAL STRATEGY, but considers the added benefit to be not proven based on these results.

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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