



IQWiG Reports – Commission No. A18-28

# **Tofacitinib (rheumatoid arthritis) –**

**Benefit assessment according to §35a  
Social Code Book V<sup>1</sup>  
(expiry of the decision)**

**Extract**

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<sup>1</sup> Translation of the executive summary of the dossier assessment *Tofacitinib (Rheumatoide Arthritis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 July 2018). Please note: This document was translated by an external translator and 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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## Executive summary of the benefit assessment

### Background

In accordance with §35a Social Code Book (SBG) 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 is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the “company”). The dossier was sent to IQWiG on 2 May 2018.

### Research question

The aim of this report is 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 who received no prior treatment with a biologic disease-modifying antirheumatic drug (bDMARD) and are indicated for initial treatment with a bDMARD.

In accordance with the G-BA’s justification paper on the initial assessment of tofacitinib, these criteria correspond to the patient populations of research questions 2 and 3 of the initial assessment A17-18 and the associated addendum A17-43. In line with the G-BA’s rationale on imposing time limits for the decisions, the research question refers exclusively to the combination therapy of tofacitinib plus MTX. In accordance with the ACT specified by the G-BA, the research question presented in Table 2 results for this benefit assessment.

Table 2<sup>2</sup>: Research questions of the benefit assessment of tofacitinib

Research question	Indication	ACT <sup>a</sup>
1	Combination therapy tofacitinib + MTX <ul style="list-style-type: none"> <li>▪ Patients with moderate to severe active rheumatoid arthritis who had received no prior bDMARD treatment and are indicated for initial treatment with a bDMARD<sup>b</sup></li> </ul>	bDMARD in combination with MTX ( <b>adalimumab</b> 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
<p>a: Presentation of the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in <b>bold</b>.</p> <p>b: In accordance with the G-BA’s justification paper on the initial assessment of tofacitinib, this corresponds to the patient populations of research questions 2 and 3 of the initial assessment A17-18 and the associated addendum A17-43. Patients with poor prognostic factors who inadequately responded to prior treatment with 1 cDMARD as well as patients who inadequately responded to prior treatment with multiple cDMARDs (including MTX).</p> <p>ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; cDMARD: classic disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate</p>		

<sup>2</sup> Table numbers start with “2” as numbering follows that of the full dossier assessment.

The company followed the G-BA's specification of the ACT. It chose adalimumab from the presented treatment options.

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

## **Results**

### ***Study pool and study characteristics***

Like the initial assessment, the benefit assessment included the two studies ORAL STANDARD and ORAL STRATEGY. Both studies were known from the initial assessment of tofacitinib. Due to the G-BA combining the relevant patient populations from the initial assessment, the subpopulation to be assessed, i.e. the relevant subpopulation for this benefit assessment, differs from that of the initial assessment.

Both studies are randomized, multicentre, double-blind, parallel-group phase III (ORAL STANDARD) or phase IIIb/IV (ORAL STRATEGY) studies. They each included adult patients with active rheumatoid arthritis and inadequate response to MTX.

In the ORAL STANDARD study, 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 this assessment, only the study arms tofacitinib 5 mg bid + MTX and adalimumab + MTX are relevant; therefore, the description below refers only to these two study arms.

In the ORAL STRATEGY study, a total of 1152 patients were randomly allocated to the arms tofacitinib (386 patients), tofacitinib + MTX (378 patients), and adalimumab + MTX (388 patients). For this assessment, only the study arms tofacitinib + MTX and adalimumab + MTX are relevant; therefore, the description below refers only to these two study arms.

In in the intervention arms of both studies, tofacitinib was administered, as approved, twice daily as a 5 mg oral tablet; subcutaneous placebo injection was administered every 2 weeks. In the comparator arm, adalimumab was administered as subcutaneous injection every 2 weeks, as approved; placebo was administered as an oral tablet twice daily. All patients additionally received MTX therapy.

In both studies, the planned treatment period was 12 months.

### ***Relevant patient population***

The total populations of the included studies comprised patients who were treated with a bDMARD for the first time. They are relevant for this assessment and represent the combination

of two subpopulations of the initial assessment. Both studies also included patients with prior bDMARD treatment, who are not relevant for this research question.

Since the total populations and the combined relevant subpopulations differ by less than 20%, data of the total population can be used alternatively if necessary. In situations where conclusions regarding the relevant subpopulation cannot be drawn with sufficient certainty on the basis of the total population, analyses of the relevant subpopulation were calculated and used.

### **Risk of bias**

The risk of bias on the study level is assessed as low for both studies. In both studies, the risk of bias is assessed as low for all-cause mortality and the outcome discontinuation due to AEs. The risk of bias for all further AE outcomes was rated as high in the ORAL STANDARD study and as low in the ORAL STRATEGY study. For all outcomes on morbidity and health-related quality of life, the risk of bias was rated as high in both studies.

### **Results**

#### ***Overall survival***

In the studies ORAL STANDARD and ORAL STRATEGY, 1 death occurred in the total populations of the study arms relevant for this benefit assessment. For this outcome, this resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

#### ***Morbidity – remission***

For the outcome remission, none of the included operationalizations (Clinical Disease Activity Index [CDAI]  $\leq 2.8$ ; Simplified Disease Activity Index [SDAI]  $\leq 3.3$  and Boolean definition) showed a statistically significant difference between treatment groups. For this outcome, there was therefore no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

#### ***Morbidity – low disease activity***

For the outcome low disease activity, the operationalization Disease-Activity-Score-28-4 erythrocyte sedimentation rate (DAS28-4 ESR)  $\leq 3.2$  in the meta-analysis of the total populations of both studies showed a statistically significant difference between treatment groups to the disadvantage of tofacitinib + MTX. For the meta-analysis of the relevant subpopulation, this effect is also significant, but it is not consistent throughout the sensitivity analyses. However, the effect to the disadvantage of tofacitinib + MTX is not confirmed by the operationalization DAS28-4 C-reactive protein (DAS28-4 CRP)  $\leq 3.2$  or the operationalizations SDAI  $\leq 11$  or CDAI  $\leq 10$ . The latter (CDAI  $\leq 10$ ) is the only operationalization without a marker of inflammation (CRP or ESR) and is therefore unaffected by substance-specific effects on these laboratory values without clinical correlate.

Overall, for the outcome low disease activity, there was therefore no hint of an added benefit or lesser benefit of tofacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

***Other morbidity outcomes***

For each of the other included morbidity outcomes:

- Tender joints
- Swollen joints
- Pain (measured using a visual analogue scale [VAS])
- Global rating of disease activity by the patient (VAS)
- Fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-Fatigue])
- Physical functioning (Health Assessment Questionnaire-Disability Index [HAQ-DI])
- Sleep disturbances (Medical Outcome Study [MOS] sleep score)
- Health status (EuroQol 5 Dimensions [EQ-5D]-VAS)

no statistically significant difference between treatment groups was found. For these outcomes, there was therefore no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

***Health-related quality of life – SF-36v2 acute***

For the physical and mental sum scores of the Short Form 36 – Version 2 Health Survey (SF-36v2) acute, no statistically significant difference between treatment groups was found. For this outcome, there was therefore no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

***Adverse events – SAEs, discontinuation due to AEs, infections***

For each of the outcomes serious adverse events (SAEs), discontinuation due to adverse events (AEs) and infections, no statistically significant difference between treatment groups was found. For these outcomes, there was therefore no hint of greater or lesser harm of tofacitinib + MTX in comparison with adalimumab + MTX; therefore, there is no proof of greater or lesser harm.

***Adverse events – serious infections***

For the outcome serious infections, a statistically significant difference between treatment groups to the disadvantage of tofacitinib + MTX was found both for the total population and the relevant subpopulation. For this outcome, this results in an indication of greater harm of tofacitinib + MTX in comparison with adalimumab + MTX.

### Probability and extent of added benefit, patient groups with therapeutically important added benefit<sup>3</sup>

On the basis of the results presented, the probability and extent of the added benefit of the drug tofacitinib compared with the ACT is assessed as follows:

For patients with moderate to severe active rheumatoid arthritis who received no prior bDMARD treatment and are indicated for initial treatment with a bDMARD, an exclusively negative effect of tofacitinib + MTX was found for serious infections. In addition to SAEs, serious infections are a major reason for imposing a time limit for the initial assessment of tofacitinib in bDMARD-naive patients. Overall, the re-assessment of tofacitinib resulted in an indication of lesser benefit of tofacitinib + MTX in comparison with adalimumab + MTX.

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

Indication	ACT <sup>a</sup>	Probability and extent of added benefit
Combination therapy tofacitinib + MTX ▪ Patients with moderate to severe active rheumatoid arthritis who received no prior DMARD treatment and who are indicated for initial treatment with a bDMARD <sup>b</sup>	bDMARD in combination with MTX ( <b>adalimumab</b> 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	Indication of lesser benefit
a: Presentation of the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in <b>bold</b> . b: In accordance with the G-BA's justification paper on the initial assessment of tofacitinib, this corresponds to the patient populations of research questions 2 and 3 of the initial assessment A17-18 and the associated addendum A17-43. Patients with poor prognostic factors who inadequately responded to prior treatment with 1 cDMARD as well as patients who inadequately responded to prior treatment with multiple cDMARDs (including MTX). ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; cDMARD: classic disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: Methotrexate		

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

<sup>3</sup> 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].



**Note:**

An addendum (A18-56) to dossier assessment A18-28 has been published.

### References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 04 June 2018]. URL: [https://www.iqwig.de/download/General-Methods\\_Version-5-0.pdf](https://www.iqwig.de/download/General-Methods_Version-5-0.pdf).
2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. *Biom J* 2015; 58(1): 43-58

*The full report (German version) is published under <https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-28-tofacitinib-rheumatoid-arthritis-benefit-assessment-according-to-35a-social-code-book-v-expiry-of-the-decision.9567.html>.*