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Tofacitinib (rheumatoid arthritis) –

Addendum to Commission A17-18[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACPA	anti-citrullinated peptide antibody
ACR	American-College-of-Rheumatology
ACT	appropriate comparator therapy
AEs	adverse events
CDAI	Clinical Disease Activity Index
cDMARD	conventional disease-modifying antirheumatic drug
CRP	c-reactive protein
DAS28	Disease-Activity-Score-28
DAS28-4 CRP	DAS28-4 C-reactive protein
DAS28-4 ESR	Disease-Activity-Score-28-4-erythrocyte sedimentation rate
EQ-5D	European Quality of Life Questionnaire 5 Dimensions
ESR	erythrocyte sedimentation rate
FACIT	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)
ITT	intention to treat
MOS	Medical Outcome Study
MTX	methotrexate
PT	Preferred Term
RCT	randomized controlled trial
SAEs	serious adverse events
SDAI	Simplified Disease Activity Index
SF-36v2	Short Form 36 – Version 2 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 4 September 2017, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-18 (Tofacitinib – Benefit assessment according to §35a Social Code Book [SGB] V [1]).

For dossier assessment A17-18, the pharmaceutical company (hereinafter referred to as "the company") presented the results of the randomized controlled trial (RCT) ORAL STANDARD. This study was suitable for the derivation of conclusions on the added benefit of tofacitinib in comparison with the appropriate comparator therapy (ACT) for research questions 2 and 3 of the benefit assessment on the basis of subpopulations. In its dossier, the company provided no data for the additionally identified RCT ORAL STRATEGY that is potentially relevant for the comparison of tofacitinib + methotrexate (MTX) vs. tofacitinib monotherapy vs. adalimumab + MTX in patients with moderate to severe active rheumatoid arthritis. According to the company, results of this study were still pending [2].

With its written comments [3], the company submitted first data on the ORAL STRATEGY study, further analyses on the ORAL STANDARD study as well as meta-analyses of both studies. The G-BA commissioned IQWiG with the assessment of the subsequently presented data on research questions 2 and 3 of dossier assessment A17-18.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

With its written comments [3], the company submitted the following data relevant for the present assessment:

- results of the ORAL STRATEGY study
- further analyses on the ORAL STANDARD study (analyses as per status of January 2017 that were not included in the dossier, as well as new analyses)
- meta-analyses of the studies ORAL STRATEGY and ORAL STANDARD

With the subsequently submitted data on the ORAL STANDARD study, the company addressed individual questions, but not all issues raised in dossier assessment A17-18. Nor did the company submit a complete analysis of all adverse events (AEs) at the System Organ Class (SOC) and Preferred Term (PT) levels for the relevant subpopulations. It also presented no such data for the ORAL STRATEGY study.

Hereinafter, the assessment of the subsequently submitted data will be carried out separately for the research questions of dossier assessment A17-18, namely as follows:

- in Section 2.1 for research question 2: patients with poor prognostic factors and inadequate response to pretreatment with 1 conventional disease-modifying antirheumatic drug (cDMARD)
- in Section 2.2 for research question 3: patients with inadequate response to pretreatment with several cDMARDs

Section 2.3 conclusively summarizes the results of the benefit assessment under consideration of dossier assessment A17-18 and the present addendum.

2.1 Research question 2: patients with poor prognostic factors and inadequate response to pretreatment with 1 cDMARD

The ORAL STANDARD study was already the basis of dossier assessment A17-18 [1]. Information on the study and patient characteristics can be found in the dossier assessment.

Table 1 and Table 2 describe the ORAL STRATEGY study used for the benefit assessment.

Table 1: Characteristics of the ORAL STRATEGY study – 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 STRATEGY	RCT, double-blind, parallel	Adult patients with active rheumatoid arthritis and ▪ inadequate response under treatment with MTX ▪ continuous administration of MTX for ≥ 4 months ▪ Oral application of MTX (15 mg to 25 mg per week) ≥ 6 weeks before the first administration of the study medication (switch from parenteral MTX to oral MTX for ≥ 6 weeks)	tofacitinib 5 mg bid (N = 386)[b] tofacitinib 5 mg bid + MTX (N = 378) adalimumab 40 mg + MTX (N = 388) Relevant analysed subpopulation thereof[c]: tofacitinib 5 mg bid + MTX (N = 241) adalimumab 40 mg + MTX (n = 216)	Screening: up to 52 days Treatment: 12 months Observation: 28 days after the last administration of the study medication (safety)	186 centres in Argentina, Australia, Bosnia and Herzegovina, Bulgaria, Canada, Chile, Czech Republic, Estonia, Israel, Korea, Latvia, Lithuania, Mexico, Peru, Philippines, Poland, Romania, Russia, Spain, South Africa, Taiwan, Thailand, Turkey, USA, United Kingdom 08/2014–12/2016	Primary: ▪ ACR 50 at month 6 Secondary: ▪ Morbidity ▪ health-related quality of life ▪ AEs

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.
b: The arm is not relevant for the assessment and is no longer shown in the next tables.
c: Patients with poor prognostic factors who have responded inadequately to prior treatment with 1 cDMARD.
ACR: American College of Rheumatology; AE: adverse event; BID: twice daily; cDMARD: conventional disease-modifying antirheumatic drug; MTX: methotrexate; n: relevant subpopulation; N: number of randomized (included) patients; RCT: randomized controlled trial; vs.: versus

Table 2: Characteristics of the intervention – RCT, direct comparison: tofacitinib + MTX versus adalimumab + MTX

Study	Intervention	Comparison
ORAL STRATEGY	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 MTX therapy having been maintained for ≥ 4 months (15–25 mg/week), switch from parenteral MTX to oral MTX therapy at a stable dose for ≥ 6 before administration of the first study medication ▪ Folic acid supplement ▪ Zoster vaccine: visit 1 (28 days before the first study medication) in patients ≥ 50 years ▪ Booster of all recommended vaccinations before the start of the study is suggested ▪ 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 ▪ Intraarticular (IA) corticosteroids were allowed as of the study visit at month 6 (in ≤ 2 joints) **Non-permitted concomitant medication:** ▪ Intramuscular (IM) and intravenous (IV) corticosteroids, biologics[b] and DMARDs (excl. MTX)[b] ▪ cytochrome P450 3A (CYP3A) and cytochrome P450 2C16 (CYP2C16) inhibitors and CYP3A inducers	

a: The following total doses were not to be exceeded: paracetamol: locally approved dosage; opiates: ≥ 30 mg/day morphine (orally); administration of opiates/paracetamol as rescue therapy was possible on ≤ 10 consecutive days, otherwise, the study had to be discontinued.
b: Biologics and DMARDs (excl. MTX) had to be discontinued 4 to 20 weeks or 1 year (rituximab) before the start of the study.
DMARDs: conventional disease-modifying antirheumatic drug; excl.: excluding, IA: intraarticular; IM: intramuscular; IV: intravenous; ND: no data; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; vs.: versus

The ORAL STRATGEY 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 1152 patients were randomly allocated to the arms tofacitinib (386 patients), tofacitinib + MTX (378 patients) and adalimumab + MTX (388 patients). For the present assessment, the study arms tofacitinib + 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. All patients received concomitant oral MTX treatment.

The planned treatment period was 12 months.

Primary outcome of the ORAL STRATEGY study was the 50% improvement in American-College-of-Rheumatology (ACR) criteria (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.

Relevant subpopulation for research question 2

The respective 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 subpopulations of the ORAL STANDARD and ORAL STRATEGY studies comprised patients who showed inadequate response only to the cDMARD MTX (for prognostic factors of the patients, see section on patient characteristics).

According to the company, these relevant subpopulations include 81 patients in the intervention arm and 76 patients in the comparator arm of the ORAL STANDARD study (see also dossier assessment A17-18), as well as 241 or 216 patients in the corresponding study arms of the ORAL STRATEGY study.

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

Patient characteristics

Table 3 shows the characteristics of the patients in the relevant subpopulation of the ORAL STRATEGY study. Information for the ORAL STANDARD study can be found in dossier assessment A17-18.

Table 3: Characteristics of the study population – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 2)

Study Characteristics Category	**Tofacitinib + MTX**	**Adalimumab + MTX**
ORAL STRATEGY	N[a] = 241	N[a] = 216
Age [years], mean (SD)	51 (14)	51 (13)
Sex [F/M], %	83/17	82/18
Region, n (%)		
Europe	109 (45.2)	90 (41.7)
USA/Canada	48 (19.9)	41 (19.0)
Latin America	63 (26.1)	62 (28.7)
Other	21 (8.7)	23 (10.6)
Disease duration: time between first diagnosis and randomization [years], mean (SD)	7.1 (6.7)	7.9 (7.6)
Functional status [HAQ-DI], mean (SD)	1.6 (0.6)	1.6 (0.6)
Tender joint count[b], mean (SD)	16.2 (6.3)	15.7 (6.8)
Swollen joint count[b], mean (SD)	12.2 (5.6)	11.3 (5.3)
Rheumatoid factor status, n (%)		
Positive	103 (42.7)	98 (45.4)
Negative	70 (29.0)	52 (24.1)
Unknown	68 (28.2)	66 (30.6)
ACPA status, n (%)		
Positive	126 (52.3)	114 (52.8)
Negative	48 (19.9)	39 (18.1)
Unknown	67 (27.8)	63 (29.2)
DAS28-4 (ESR), n (%)		
< 2.6	0 (0)	0 (0)
2.6–3.2	0 (0)	0 (0)
> 3.2 to ≤ 5.1	12 (5.0)	20 (9.3)
≥ 5.1	227 (94.2)	194 (89.8)
Unknown	2 (0.8)	2 (0.9)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation[c], 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 28 joints.
c: Study discontinuation in the total study population: tofacitinib n = 73 (19.4%) of 376; adalimumab n = 74 (19.2%) of 386

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 51 years. Markedly more women (> 80%) than men were included in both arms.

At least half of the patients was seropositive (positive rheumatoid factor serostatus and/or positive anti-citrullinated peptide antibodies [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

Table 4 shows the risk of bias at study level.

Table 4: 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
ORAL STRATEGY	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for the ORAL STRATEGY study as well as for the ORAL STANDARD study.

2.1.1 Results on added benefit

Outcomes included and risk of bias

The patient-relevant outcomes to be included in the assessment should principally be the same as those included in A17-18 [1]. The patient-relevant outcome “health status” was additionally recorded in the ORAL STRATEGY study (recorded with the visual analogue scale [VAS] of the European Quality of Life Questionnaire 5 Dimensions [EQ-5D]).

Table 5 shows for which outcomes data were available for the relevant subpopulation of the studies included. Table 6 describes the risk of bias for the relevant outcomes.

Table 5: Matrix of outcomes – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 2)

Study	Endpoints															
	All-cause mortality	**Remission (CDAI ≤ 2.8; SDAI ≤ 3.3; Boolean definition)**	**Low disease activity (DAS28-4 ESR ≤ 3.2, DAS28-4 CRP ≤ 3.2, CDAI ≤ 10, SDAI ≤ 11)**	**Tender joints[a]**	**Swollen joints[a]**	**Pain (VAS)**	**Disease activity (VAS)**	**Health status (EQ-5D 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[c]**
ORAL STANDARD	No[d]	Yes	Yes	Yes	Yes	Yes	Yes	No[e]	Yes	Yes	No[f]	Yes	Yes	Yes	Yes	Yes
ORAL STRATEGY	No[d]	Yes	Yes	Yes	Yes	Yes	Yes	No[d]	Yes	Yes	No[g]	Yes	Yes	Yes	Yes	Yes

a: Based on 28 joints.
b: Any AEs of the SOC "infections and infestations".
c: Any SAE of the SOC "infections and infestations".
d: The company did not present data for the subpopulation.
e: Outcome not recorded in the ORAL STANDARD study.
f: The available data were not usable; see dossier assessment A17-18 for reasons [1].
g: Outcome not recorded in the ORAL STRATEGY study.

AE: adverse event; CDAI: Clinical Disease Activity Index; CRP: c-reactive protein; DAS28: Disease-Activity-Score-28; EQ-5D: European Quality of Life-5 Dimensions; ESR: erythrocyte sedimentation rate; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; MOS: Medical Outcome Study; MTX: methotrexate; RCT: randomized controlled trial; SDAI: Simplified Disease Activity Index; SF-36v2: Short Form 36 – version 2 Health Survey; SAE: serious adverse event; DAI: Simplified Disease Activity Index; VAS: visual analogue scale; vs.: versus

Table 6: Risk of bias at study and outcome level – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 2)

Study	Study level	Endpoints															
		All-cause mortality	Remission (CDAI ≤ 2.8; SDAI ≤ 3.3; Boolean definition)	Low disease activity (DAS28-4 ESR ≤ 3.2, DAS28-4 CRP ≤ 3.2, DAS, CDAI ≤ 10, SDAI ≤ 11)	Tender joints[a]	Swollen joints[a]	Pain (VAS)	Disease activity (VAS)	Health status (EQ-5D 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[c]
ORAL STANDARD	L	–[d]	H[e]	H[e]	H[e]	H[e]	H[e]	H[e]	–[f]	H[e]	H[e]	–[g]	H[e]	H[i]	L	H[i]	H[i]
ORAL STRATEGY	L	–[d]	H[e]	H[e]	H[e]	H[e]	H[e]	H[e]	–[d]	H[e]	H[e]	–[h]	H[e]	H[i]	L	H[i]	H[i]

a: Based on 28 joints.
b: Any AEs of the SOC "infections and infestations".
c: Any SAE of the SOC "infections and infestations".
d: The company did not present data for the subpopulation.
e: Large proportion of values imputed (> 15%).
f: Outcome not recorded in the ORAL STANDARD study.
g: The available data were not usable, see dossier assessment A17-18 for reasons [1].
h: Outcome not recorded in the ORAL STRATEGY study.
i: Unclear proportion of patients who were not completely observed.

AE: adverse event; CDAI: Clinical Disease Activity Index; CRP: c-reactive protein; DAS28: Disease-Activity-Score-28; EQ-5D: European Quality of Life-5 Dimensions; ESR: erythrocyte sedimentation rate; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; H: high; HAQ-DI: Health Assessment Questionnaire-Disability Index; L: low; MOS: Medical Outcome Study; MTX: methotrexate; RCT: randomized controlled trial; SDAI: Simplified Disease Activity Index; SF-36v2: Short Form 36 – version 2 Health Survey; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The risk of bias for the outcome “discontinuation due to adverse events” was rated as low in both studies and as high for all other outcomes for which analyses were available for the relevant subpopulation.

In both studies, 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 was > 15%. However, the effects of the imputations could not be estimated and the intention-to-treat (ITT) principle was therefore not adequately implemented. The high risk of bias for the AE outcomes “SAEs”, “infections” and “serious infections” resulted from the unclear proportion of not completely observed patients.

Results

Table 7 and Table 8 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.

The data of the studies ORAL STANDARD and ORAL STRATEGY were pooled in a meta-analysis. In the present data situation, models with a fixed effect are used. The models with random effects that were also presented by the company with its written comments did not show other qualitative results.

Where necessary, the data from the company’s dossier were supplemented with the Institute’s calculations.

Table 7: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 2)

Outcome category Outcome Study	Tofacitinib + MTX		Adalimumab + MTX		Tofacitinib + MTX vs. adalimumab + MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality					
ORAL STANDARD	79	0 (0)	75	ND[a]	–
ORAL STRATEGY	241	ND[b]	216	0 (0)	–
Morbidity – proportion of patients with improvement					
Remission					
CDAI ≤ 2.8					
ORAL STANDARD	79	12 (15.2)	75	7 (9.3)	1.63 [0.68; 3.91]; 0.288
ORAL STRATEGY	241	40 (16.6)	216	41 (19.0)	0.87 [0.59; 1.30]; 0.505
Total[c]					0.98 [0.69; 1.40]; 0.919
SDAI ≤ 3.3					
ORAL STANDARD	79	12 (15.2)	75	6 (8.0)	1.90 [0.75; 4.80]; 0.176
ORAL STRATEGY	241	35 (14.5)	216	38 (17.6)	0.83 [0.54; 1.26]; 0.372
Total[c]					0.97 [0.66; 1.41]; 0.868
Boolean definition					
ORAL STANDARD	79	7 (8.9)	75	4 (5.3)	1.66 [0.51; 5.45]; 0.402
ORAL STRATEGY	241	30 (12.5)	216	28 (13.0)	0.96 [0.59; 1.55]; 0.869
Total[c]					1.05 [0.67; 1.63]; 0.843
Low disease activity					
DAS28-4 (ESR ≤ 3.2)					
ORAL STANDARD	70	16 (22.9)	64	19 (29.7)	0.77 [0.43; 1.36]; 0.530
ORAL STRATEGY	241	65 (27.0)	216	79 (36.6)	0.74 [0.56; 0.97]; 0.028
Total[c]					0.74 [0.58; 0.95]; 0.018

(continued)

Table 7: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 2) (continued)

Outcome category Outcome Study	Tofacitinib + MTX		Adalimumab + MTX		Tofacitinib + MTX vs. adalimumab + MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Morbidity – proportion of patients with improvement					
DAS28-4 (CRP ≤ 3.2)					
ORAL STANDARD	79	40 (50.6)	75	34 (45.3)	1.12 [0.80; 1.55]; 0.512
ORAL STRATEGY	241	113 (46.9)	216	118 (54.6)	0.86 [0.72; 1.03]; 0.098
Total[c]					0.91 [0.78; 1.07]; 0.272
SDAI ≤ 11					
ORAL STANDARD	79	39 (49.4)	75	32 (42.7)	1.16 [0.82; 1.63]; 0.407
ORAL STRATEGY	241	121 (50.2)	216	118 (54.6)	0.92 [0.77; 1.09]; 0.344
Total[c]					0.97 [0.83; 1.13]; 0.690
CDAI ≤ 10					
ORAL STANDARD	79	40 (50.6)	75	30 (40.0)	1.27 [0.89; 1.80]; 0.190
ORAL STRATEGY	241	122 (50.6)	216	116 (53.7)	0.94 [0.79; 1.12]; 0.510
Total[c]					1.01 [0.86; 1.18]; 0.925
Tender joints[d] (≤ 1)					
ORAL STANDARD	79	24 (30.4)	75	22 (29.3)	1.04 [0.64; 1.68]; 0.922
ORAL STRATEGY	241	87 (36.1)	216	85 (39.4)	0.92 [0.72; 1.16]; 0.474
Total[c]					0.94 [0.76; 1.16]; 0.575
Swollen joints[d] (≤ 1)					
ORAL STANDARD	79	36 (45.6)	75	34 (45.3)	1.01 [0.71; 1.42]; > 0.999
ORAL STRATEGY	241	123 (51.0)	216	119 (55.1)	0.93 [0.78; 1.10]; 0.385
Total[c]					0.94 [0.81; 1.10]; 0.462

(continued)

Table 7: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 2) (continued)

Outcome category Outcome Study	Tofacitinib + MTX		Adalimumab + MTX		Tofacitinib + MTX vs. adalimumab + MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Morbidity – proportion of patients with improvement					
Fatigue (FACIT-Fatigue)[e]					
ORAL STANDARD	79	37 (46.8)	75	41 (54.7)	0.86 [0.63; 1.17]; 0.515
ORAL STRATEGY	241	150 (62.2)	216	124 (57.4)	1.08 [0.93; 1.26]; 0.295
Total[c]					1.03 [0.90; 1.18]; 0.683
Physical functioning (HAQ-DI)[f]					
ORAL STANDARD	79	49 (62.0)	75	49 (65.3)	0.95 [0.75; 1.21]; 0.718
ORAL STRATEGY	241	150 (62.4)	216	143 (66.2)	0.94 [0.82; 1.08]; 0.377
Total[c]					0.94 [0.84; 1.06]; 0.945
Side effects					
AEs (supplementary information)					
ORAL STANDARD	83	61 (73.5)	78	53 (67.9)	–
ORAL STRATEGY	241	140 (58.1)	216	139 (64.4)	–
SAEs					
ORAL STANDARD	83	13 (15.7)	78	4 (5.1)	3.05 [1.04; 8.97]; 0.030
ORAL STRATEGY	241	17 (7.1)	216	13 (6.0)	1.17 [0.58; 2.36]; 0.656
Total[c]					1.61 [0.91; 2.85]; 0.104
Discontinuation due to AEs					
ORAL STANDARD	83	8 (9.6)	78	5 (6.4)	1.50 [0.51; 4.40]; 0.532
ORAL STRATEGY	241	14 (5.8)	216	23 (10.7)	0.55 [0.29; 1.03]; 0.063
Total[c]					0.71 [0.42; 1.22]; 0.217

(continued)

Table 7: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 2) (continued)

Outcome category Outcome Study	Tofacitinib + MTX		Adalimumab + MTX		Tofacitinib + MTX vs. adalimumab + MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Side effects					
Infections[g]					
ORAL STANDARD	83	35 (42.2)	78	25 (32.1)	1.32 [0.87; 1.98]; 0.224
ORAL STRATEGY	241	68 (28.2)	216	62 (28.7)	0.98 [0.73; 1.32]; 0.908
Total[c]					1.08 [0.85; 1.37]; 0.539
Serious infections[h]					
ORAL STANDARD	83	3 (3.6[i])	78	0 (0)[i]	6.58 [0.35; 125.43][j]; ND
ORAL STRATEGY	241	7 (2.9[i])	216	5 (2.3[i])	1.25 [0.40; 3.90]; ND
Total[c]					1.73 [0.63; 4.78]; 0.291

a: At most 1 patient in the adalimumab arm, it is unclear whether the death occurred in this subpopulation.
b: At most 2 patients in the tofacitinib arm, it is unclear whether the deaths occurred in this subpopulation.
c: Meta-analysis with a model with fixed effect according to Mantel-Haenzsel.
d: Based on 28 joints.
e: Patients with improvement by ≥ 4 points.
f: Patients with improvement by ≥ 0.22 points.
g: Any AE of the SOC "infections and infestations".
h: Any SAE of the SOC "infections and infestations".
i: Institute's calculation.
j: Institute's calculation with correction factor 0.5 in both study arms.

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; AE: adverse event; CI: confidence interval; MTX: methotrexate; n: number of patients with (at least 1) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; ; SAE: serious adverse event; SDAI: Simplified Disease Activity Index; vs.: versus

Table 8: Results (morbidity and health-related quality of life, continuous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 2)

Outcome category **Outcome** **Study**	**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]**
Morbidity							
Pain (VAS)[c]							
ORAL STANDARD	60	56.2 (20.9)	−29.7 (28.3)	61	57.3 (24.4)	−29.1 (25.5)	−2.60 [−10.32; 5.12]; 0.509
ORAL STRATEGY	201	60.1 (23.0)	−33.4 (26.6)	174	61.7 (21.8)	−33.5 (29.8)	−0.38 [−4.75; 4.00]; 0.866
Total[d]							−0.92 [−4.73; 2.89]; 0.636
Disease activity (VAS)[c]							
ORAL STANDARD	60	58.1 (21.7)	−29.6 (31.2)	61	58.8 (23.7)	−28.0 (29.6)	−3.49 [−11.48; 4.51]; 0.392
ORAL STRATEGY	201	60.9 (22.5)	−32.6 (27.7)	174	60.1 (22.8)	−32.1 (29.4)	0.78 [−3.62; 5.18]; 0.727
Total[d]							−0.21 [−4.07; 3.64]; 0.914
Health status (EQ-5D VAS)							
ORAL STANDARD	Outcome not recorded						
ORAL STRATEGY	No usable data						
Sleep disturbances (MOS sleep scale)							
ORAL STANDARD	No usable data						
ORAL STRATEGY	Outcome not recorded						

(continued)

Table 8: Results (morbidity and health-related quality of life, continuous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 2)(continued)

Outcome category **Outcome** **Study**	**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]**
Health-related quality of life							
SF-36v2 acute[e]							
Physical sum score							
ORAL STANDARD	79	33.3 (7.8)	8.2 (8.4)[f]	75	31.8 (6.5)	9.0 (7.9)[f]	0.91 [−1.58; 3.41]; 0.472
ORAL STRATEGY	199	31.9 (6.9)	9.2 (7.9)	173	31.9 (7.6)	8.5 (8.6)	0.63 [−0.86; 2.11]; 0.407
Total[d]							0.70 [−0.57; 1.98]; 0.280
Mental sum score							
ORAL STANDARD	79	39.7 (12.8)	4.3 (9.0)[f]	75	39.9 (11.6)	3.6 (11.2)[f]	0.81 [−2.22; 3.84]; 0.597
ORAL STRATEGY	199	38.5 (10.9)	6.5 (10.2)	173	39.2 (11.5)	6.8 (11.5)	−0.85 [−2.65; 0.95]; 0.354
Total[d]							−0.42 [−1.96; 1.13]; 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 deterioration.
d: Meta-analysis with a model with fixed effect with inverted variance.
e: Higher values indicate improvement.
f: Based on patients for whom values were available at month 12, N = 59 (75%) vs. N = 61 (77%).
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions: MD: mean difference; 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

Two relevant studies were available for the assessment of the added benefit of tofacitinib. In view of the low risk of bias, at most a proof of an added benefit can be derived for the outcome “discontinuation due to AEs”. For all other outcomes, at most indications 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 of the ORAL STANDARD study died during the observation period in the relevant study arms, namely in the adalimumab arm. Two patients of the total study population of the ORAL STRATEGY study died during the observation period in the tofacitinib 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

No statistically significant difference between the treatment groups was shown for the outcome "remission" for any of the operationalizations (CDAI ≤ 2.8; SDAI ≤ 3.3 and Boolean definition). 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.

Low disease activity

The ORAL STRATEGY study and the meta-analysis of both studies showed a statistically significant difference to the disadvantage of tofacitinib + MTX for the outcome "low disease activity" for the operationalization Disease-Activity-Score-28-4-erythrocyte sedimentation rate (DAS28-4 ESR) ≤ 3.2. This effect was neither confirmed by the operationalization DAS28-4 C-reactive protein (DAS28-4 CRP) ≤ 3.2 nor by the operationalizations SDAI ≤ 11 or CDAI ≤ 10. The latter (CDAI ≤ 10) was the only operationalization that did not include a recording of an inflammation parameter (CRP or ESR) and was therefore uninfluenced by substance-specific effects on these laboratory values without clinical correlate.

In summary, this resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for the outcome "low disease activity"; an added benefit is therefore not proven.

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.

Pain (VAS)

For the outcome "pain" (VAS), 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 this outcome; an added benefit is therefore not proven.

Disease activity (VAS)

For the outcome "disease activity" (VAS), 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 this outcome; an added benefit is therefore not proven.

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.

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.

Sleep disturbances (MOS sleep scale)

There were no usable data for the outcome "sleep disturbances" (MOS sleep scale) for the ORAL STANDARD study. This outcome was not recorded in the STRATEGY study. 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.

Health-related quality of life

Short Form 36 – version 2 Health Survey (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 differences between the treatment groups were 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.

Side effects

SAEs, discontinuation due to AEs and infections

No statistically significant difference between the treatment groups was shown for any of the following outcomes: SAEs, discontinuation due to AEs, infections and serious infections (AEs and SAEs of the SOC "infections and infestations"). Hence, for these outcomes, there

was no hint of greater or lesser harm from tofacitinib + MTX in comparison with adalimumab + MTX; greater or lesser harm is therefore not proven.

Further specific AEs

The company presented no complete analysis of the AEs at SOC and PT level for either of both relevant studies for the relevant subpopulation.

Subgroups and other effect modifiers

For the ORAL STANDARD study, dossier assessment A17-18 [1] showed an effect modification relevant for the conclusion only for the subgroup characteristic "age", namely for the outcome "SAE". Based on these results, consideration of the subgroups is restricted to the characteristic "age" in the present addendum.

For research question 2 of the ORAL STRATEGY study, no statistically significant interaction between the treatment and the subgroup characteristic "age" (p-value < 0.05) is available for any of the outcomes with usable data. Accordingly, no consistent picture between the studies was shown for the outcome "SAE": The ORAL STANDARD study shows a statistically significant difference to the disadvantage of tofacitinib for patients ≤ 65 years. However, the larger study ORAL STRATEGY also demonstrated a negative direction of effect, but the estimation is imprecise and the result is not statistically significant (Table 9 and Figure 1 in Appendix A). In summary, this resulted in no evidence of an effect modification for the characteristic "age"; therefore, separate derivation of effects by subgroups was omitted.

Table 9: Subgroups (side effects, dichotomous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 2)

Outcome Characteristic	Tofacitinib + MTX		Adalimumab + MTX		Tofacitinib + MTX vs. adalimumab + MTX	
Subgroup Study	N	Patients with event n (%)	N	Patients event n (%)	RR [95% CI]	p-value
SAEs						
Age						
≤ 65						
ORAL STANDARD	64	12 (18.8)	66	2 (3.0)	6.19 [1.44; 26.56]	0.004[a]
ORAL STRATEGY	210	13 (6.2)	187	10 (5.4)	1.16 [0.52; 2.58]	0.732[a]
> 65						
ORAL STANDARD	19	1 (5.3)	12	2 (16.7)	0.32 [0.03; 3.12]	0.409[a]
ORAL STRATEGY	31	4 (12.9)	29	3 (10.3)	1.25 [0.30; 5.10]	0.803[a]

a: Institute's calculation, unconditional exact test (CSZ method according to [4]).

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; SAE: serious adverse event; vs.: versus

2.1.2 Probability and extent of added benefit

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 (see Table 10). The different outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [5].

Table 10: Extent of added benefit at outcome level: tofacitinib + MTX vs. adalimumab + MTX (research question 2)

Outcome category **Outcome**	**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: ND[c]	Lesser benefit/added benefit not proven
Morbidity		
Remission		Lesser benefit/added benefit not proven
CDAI ≤ 2.8	Proportion: 15.2–16.6% vs. 9.3–19.0%[d] RR: 0.98 [0.69; 1.40]; p = 0.919	
SDAI ≤ 3.3	Proportion: 14.5–15.2% vs. 8.0–17.6%[d] RR: 0.97 [0.66; 1.41]; p = 0.868	
Boolean definition	Proportion: 8.9–12.5% vs. 5.3–13.0%[d] RR: 1.05 [0.67; 1.63]; p = 0.843	
Low disease activity		Lesser benefit/added benefit not proven
DAS28-4 ESR ≤ 3.2	Proportion: 22.9–27.0% vs. 29.7–36.6%[d] RR: 0.74 [0.58; 0.95]; p = 0.018	
DAS28-4 CRP ≤ 3.2	Proportion: 46.9–50.6% vs. 45.3–54.6%[d] RR: 0.91 [0.78; 1.07]; 0.272	
CDAI ≤ 10	Proportion: 50.6% vs. 40.0–53.7%[d] RR: 1.01 [0.86; 1.18]; p = 0.925	
SDAI ≤ 11	Proportion: 49.4–50.2% vs. 42.7–54.6%[d] RR: 0.97 [0.83; 1.13]; p = 0.690	
Tender joints (≤ 1)	Proportion: 30.4–36.1% vs. 29.3–39.4%[d] RR: 0.94 [0.76; 1.16]; p = 0.575	Lesser benefit/added benefit not proven

(continued)

Table 10: Extent of added benefit at outcome level: tofacitinib + MTX vs. adalimumab + MTX (research question 2) (continued)

Outcome category **Outcome**	**Tofacitinib + MTX vs. adalimumab + MTX** **Proportion of patients with event or change** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Morbidity (continued)		
Swollen joints (≤ 1)	Proportion: 45.6–51.0% vs. 45.3–55.1%[d] RR: 0.94 [0.81; 1.10]; p = 0.462	Lesser benefit/added benefit not proven
Pain (VAS)	Mean change between start of the study and month 12: −29.7 to −33.4 vs. −29.1 to −33.5[e] MD: −0.92 [−4.73; 2.89]; p = 0.636	Lesser benefit/added benefit not proven
Disease activity (VAS)	Mean change between start of the study and month 12: −29.6 to −32.6 vs. −28.0 to 32.1[d] MD: −0.21 [−4.07; 3.64]; p = 0.914	Lesser benefit/added benefit not proven
Fatigue (FACIT-F)[e]	Proportion: 46.8–62.2% vs. 54.7–57.4%[d] RR: 1.03 [0.90; 1.18]; p = 0.683	Lesser benefit/added benefit not proven
Physical functioning (HAQ-DI)[f]	Proportion: 62.0–62.4% vs. 65.3–66.2%[d] RR: 0.94 [0.84; 1.06]; p = 0.945	Lesser benefit/added benefit not proven
Sleep disturbances (MOS sleep scale)	No usable data[g]	Lesser benefit/added benefit not proven
EQ-5D (VAS)	No usable data[h]	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: 8.2–9.2 vs. 8.5–9.0[d] MD: 0.70 [−0.57; 1.98]; p = 0.280	Lesser benefit/added benefit not proven
Mental sum score	Mean change between start of the study and month 12: 4.3–6.5 vs. 3.6–6.8[d] MD: −0.42 [−1.96; 1.13]; p = 0.597	Lesser benefit/added benefit not proven

(continued)

Table 10: Extent of added benefit at outcome level: tofacitinib + MTX vs. adalimumab + MTX (research question 2) (continued)

Outcome category **Outcome**	**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: 7.1–15.7% vs. 5.1–6.0%[d] RR: 1.61 [0.91; 2.85]; p = 0.104	Greater/lesser harm not proven
Discontinuation due to AEs	Proportion: 5.8–9.6% vs. 6.4–10.7%[d] RR: 0.71 [0.42; 1.22]; p = 0.217	Greater/lesser harm not proven
Infections	Proportion: 28.2–42.2% vs. 28.7–32.1%[d] RR: 1.08 [0.85; 1.37]; p = 0.539	Greater/lesser harm not proven
Serious Infections	Proportion: 2.9–3.6% vs. 0–2.3%[d] RR: 1.73 [0.63; 4.78]; p = 0.291	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: The company presented no analyses for the relevant subpopulation for this outcome.
d: Minimum and maximum proportions of events or mean changes in each treatment arm in the included studies.
e: Patients with improvement by ≥ 4 points.
f: Patients with improvement by ≥ 0.22 points.
g: For the ORAL STANDARD study, the company presented no usable data for the relevant subpopulation, the outcome was not recorded in the ORAL STRATEGY study.
h: The outcome was not recorded in the ORAL STANDARD study, for the ORAL STRATEGY study, the company presented no usable data for the relevant subpopulation for this outcome.

ACR American College of Rheumatology; AE: adverse event; CDAI: Clinical Disease Activity Index; CI: confidence interval: upper limit of the Cl; DAS28: Disease-Activity-Score-28; EQ-5D: EuroQol 5 Dimensions: European Quality of Life-5 Dimensions; 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; MD: mean difference; 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

Overall conclusion on the added benefit (research question 2)

Table 11 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 11: Positive and negative effects from the assessment of tofacitinib + MTX in comparison with adalimumab + MTX (research question 2)

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 1 cDMARD and with poor prognostic factors. An added benefit is therefore not proven.

2.1.3 List of included studies

ORAL STRATEGY

Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet 2017; 390(10093): 457-468.

Pfizer. An Efficacy And Safety Study Evaluating Tofacitinib With And Without Methotrexate Compared To Adalimumab With Methotrexate [online]. In: ClinicalTrials.gov. [Accessed: 31.05.2017]. URL: https://ClinicalTrials.gov/show/NCT02187055.

Pfizer, Inc. . A PHASE 3b/4 Randomized Double Blind Study of 5 mg of Tofacitinib with and without Methotrexate in Comparison to Adalimumab with Methotrexate in Subjects with Moderately to Severely Active Rheumatoid Arthritis [online]. In: EU Clinical Trials Register. [Accessed: 31.05.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-000358-13.

Pfizer. A Phase 3b/4 Randomized Double-Blind Study of 5 mg of Tofacitinib With and Without Methotrexate in Comparison to Adalimumab With Methotrexate in Subjects With Moderately to Severely Active Rheumatoid Arthritis; study A3921187 ; full clinical study report [I:\Aufträge\AM\2017\A17-43_Tofacitinib_Addendum(A17-18)\8_KOM\2_Übersetzung]. 2017.

Pfizer. A Phase 3b/4 Randomized Double-Blind Study of 5 mg of Tofacitinib With and Without Methotrexate in Comparison to Adalimumab With Methotrexate in Subjects With Moderately to Severely Active Rheumatoid Arthritis; study A3921187 ; Zusatzanalysen [unpublished]. 2017.

The reference list for the ORAL STANDARD study can be found in dossier assessment A17-18 [1].

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

The ORAL STRATEGY study with the subpopulation relevant for the present research question is described in Table 12. The description of the ORAL STANDARD study can be found in dossier assessment A17-18.

Table 12: Characteristics of the ORAL STRATEGY study – 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 STRATEGY	RCT, double-blind, parallel	Adult patients with active rheumatoid arthritis and ▪ inadequate response under treatment with MTX ▪ continuous administration of MTX for ≥ 4 months ▪ Oral application of MTX (15 mg to 25 mg per week) ≥ 6 weeks before the first administration of the study medication (switch from parenteral MTX to oral MTX for ≥ 6 weeks)	▪ tofacitinib 5 mg bid (N = 386)[b] tofacitinib 5 mg bid + MTX (N = 378) adalimumab 40 mg + MTX (N = 388) Relevant analysed subpopulation thereof[c]: tofacitinib 5 mg bid + MTX (N = 106) adalimumab 40 mg + MTX (n = 135)	Screening: up to 52 days Treatment: 12 months Observation: 28 days after the last administration of the study medication (safety)	186 centres in Argentina, Australia, Bosnia and Herzegovina, Bulgaria, Canada, Chile, Czech Republic, Estonia, Israel, Korea, Latvia, Lithuania, Mexico, Peru, Philippines, Poland, Romania, Russian Federation, Spain, South Africa, Taiwan, Thailand, Turkey, USA, United Kingdom 08/2014–12/2016	Primary: ▪ ACR 50 at month 6 Secondary: ▪ Morbidity ▪ health-related quality of life ▪ AEs

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.
b: The arm is not relevant for the assessment and is no longer shown in the next tables.
c: Patients who have responded inadequately to prior treatment with several cDMARDs.

ACR: American College of Rheumatology; AE: adverse event; BID: twice daily; cDMARD: conventional disease-modifying antirheumatic drug; MTX: methotrexate; n: relevant subpopulation; N: number of randomized (included) patients; RCT: randomized controlled trial; vs.: versus

The characteristics of the ORAL STRATEGY study including the characteristics of the interventions are described in Section 2.1.1.

Relevant subpopulation for research question 3

The subpopulations of patients in the ORAL STANDARD and ORAL STRATEGY studies with inadequate response to prior treatment with several cDMARDs were relevant for research question 3. According to the company, these relevant subpopulations include 102 patients in the intervention arm and 104 patients in the comparator arm of the ORAL STANDARD study, as well as 106 or 135 patients in the corresponding study arms of the ORAL STRATEGY study.

Patient characteristics

Table 13 shows the characteristics of the patients in the relevant subpopulation of the ORAL STRATEGY study.

Table 13: Characteristics of the study population – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 3)

Study Characteristics Category	Tofacitinib + MTX	Adalimumab + MTX
ORAL STRATEGY	N[a] = 106	N[a] = 135
Age [years], mean (SD)	48 (13)	50 (13)
Sex [F/M], %	86/14	86/14
Region, n (%)		
Europe	34 (32.1)	47 (34.8)
USA/Canada	10 (9.4)	20 (14.8)
Latin America	25 (23.6)	26 (19.3)
Other	37 (34.9)	42 (31.1)
Disease duration: time between first diagnosis and randomization [years], mean (SD)	7.6 (7.0)	8.0 (7.0)
Functional status [HAQ-DI], mean (SD)	1.5 (0.7)	1.5 (0.7)
Tender joint count[b], mean (SD)	14.3 (6.5)	14.6 (6.6)
Swollen joint count[b], mean (SD)	11.0 (5.8)	10.9 (5.7)
Rheumatoid factor status, n (%)		
Positive	50 (47.2)	51 (37.8)
Negative	17 (16.0)	35 (25.9)
Unknown	39 (36.8)	49 (36.3)
ACPA status, n (%)		
Positive	49 (46.2)	70 (51.9)
Negative	18 (17.0)	17 (12.6)
Unknown	39 (36.8)	48 (35.6)
DAS28-4 (ESR), n (%)		
< 2.6	0 (0)	0 (0)
2.6–3.2	0 (0)	0 (0)
> 3.2 to ≤ 5.1	5 (4.7)	11 (8.1)
≥ 5.1	99 (93.4)	121 (89.6)
Unknown	2 (1.9)	3 (2.2)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation[c], 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 28 joints.
c: Study discontinuation in the total study population: tofacitinib n = 73 (19.4%) of 376; adalimumab n = 74 (19.2%) of 386

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 were balanced between the arms of the ORAL STRATEGY study in the relevant subpopulation. The mean age of the patients was about 49 years. Markedly more women (86%) than men were included in both arms.

At least half of the 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 STRATEGY study (see Table 4 in Section 2.1.1).

2.2.1 Results on added benefit

Outcomes included and risk of bias

The patient-relevant outcomes listed for research question 2 were also to be included in the assessment for research question 3 (see Section 2.1.1).

The data availability at outcome level for research question 3 and research question 2 was identical (Table 5 in Section 2.1.1).

Table 14 describes the risk of bias for the relevant outcomes.

Table 14: Risk of bias at study and outcome level – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 3)

Study	Study level	Outcomes															
		All-cause mortality	Remission (CDAI ≤ 2.8; SDAI ≤ 3.3; Boolean definition)	Low disease activity (DAS28-4 ESR ≤ 3.2, DAS28-4 CRP ≤ 3.2, DAS, CDAI ≤ 10, SDAI ≤ 11)	Tender joints[a]	Swollen joints[a]	Pain (VAS)	Disease activity (VAS)	Health status (EQ-5D 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[c]
ORAL STANDARD	L	–[d]	H[e]	H[e]	H[e]	H[e]	H[e]	H[e]	–[f]	H[e]	H[e]	–[g]	H[e]	H[i]	L	H[i]	H[i]
ORAL STRATEGY	L	–[d]	H[e]	H[e]	H[e]	H[e]	H[e]	H[e]	–[d]	H[e]	H[e]	–[h]	H[e]	H[i]	L	H[i]	H[i]

a: Based on 28 joints.
b: Any AEs of the SOC "infections and infestations".
c: Any SAE of the SOC "infections and infestations".
d: The company presented no data for the subpopulation.
e: Large proportion of values imputed (> 15%).
f: Outcome not recorded in the ORAL STANDARD study.
g: The available data were not usable, see dossier assessment A17-18 for reasons [1].
h: Outcome not recorded in the ORAL STRATEGY study.
i: Unclear proportion of patients who were not completely observed.

AE: adverse event; CDAI: Clinical Disease Activity Index; CRP: c-reactive protein; DAS28: Disease-Activity-Score-28; EQ-5D: European Quality of Life-5 Dimensions; ESR: erythrocyte sedimentation rate; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; H: high; HAQ-DI: Health Assessment Questionnaire-Disability Index; L: low; MOS: Medical Outcome Study; MTX: methotrexate; RCT: randomized controlled trial; SDAI: Simplified Disease Activity Index; SF-36v2: Short Form 36 – version 2 Health Survey; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Results

Table 15 and Table 16 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).

The data of the studies ORAL STANDARD and ORAL STRATEGY were pooled in a meta-analysis. In the present data situation, models with a fixed effect are used. The models with random effects that were also presented by the company with its written comments did not show other qualitative results.

Where necessary, the data from the company's dossier were supplemented with the Institute's calculations.

Table 15: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 3)

Outcome category Outcome Study	Tofacitinib + MTX		Adalimumab + MTX		Tofacitinib + MTX vs. adalimumab + MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality					
ORAL STANDARD	100	0 (0)	103	ND[a]	–
ORAL STRATEGY	106	ND[b]	135	0 (0)	–
Morbidity – proportion of patients with improvement					
Remission					
CDAI ≤ 2.8					
ORAL STANDARD	100	14 (14.0)	103	14 (13.6)	1.03 [0.52; 2.05]; 0.971
ORAL STRATEGY	106	27 (25.5)	135	19 (14.1)	1.81 [1.07; 3.07]; 0.028
Total[c]					1.46 [0.96; 2.21]; 0.076
SDAI ≤ 3.3					
ORAL STANDARD	100	14 (14.0)	103	17 (16.5)	0.85 [0.44; 1.63]; 0.620
ORAL STRATEGY	106	24 (22.6)	135	18 (13.3)	1.70 [0.97; 2.96]; 0.062
Total[c]					1.26 [0.83; 1.91]; 0.275
Boolean definition					
ORAL STANDARD	100	11 (11.0)	103	10 (9.7)	1.13 [0.50; 2.55]; 0.763
ORAL STRATEGY	106	19 (17.9)	135	16 (11.9)	1.51 [0.82; 2.80]; 0.187
Total[c]					1.36 [0.83; 2.21]; 0.222

(continued)

Table 15: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 3) (continued)

Outcome category Outcome Study	Tofacitinib + MTX		Adalimumab + MTX		Tofacitinib + MTX vs. adalimumab + MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Morbidity – proportion of patients with improvement					
Low disease activity					
DAS28-4 (ESR ≤ 3.2)					
ORAL STANDARD	91	17 (18.7)	91	24 (25.8)	0.72 [0.42; 1.25]; 0.245
ORAL STRATEGY	106	31 (29.3)	135	38 (28.2)	1.04 [0.70; 1.55]; 0.852
Total[c]					0.90 [0.65; 1.24]; 0.526
DAS28-4 (CRP ≤ 3.2)					
ORAL STANDARD	100	44 (44.0)	103	44 (42.7)	1.03 [0.75; 1.41]; 0.854
ORAL STRATEGY	106	48 (45.3)	135	64 (47.4)	0.96 [0.73; 1.26]; 0.743
Total[c]					0.99 [0.80; 1.21]; 0.907
SDAI ≤ 11					
ORAL STANDARD	100	45 (45.0)	103	37 (35.9)	1.25 [0.89; 1.75]; 0.190
ORAL STRATEGY	106	51 (48.1)	135	66 (48.9)	0.98 [0.76; 1.28]; 0.905
Total[c]					1.09 [0.88; 1.34]; 0.426
CDAI ≤ 10					
ORAL STANDARD	100	42 (42.0)	103	37 (35.9)	1.17 [0.83; 1.65]; 0.376
ORAL STRATEGY	106	52 (49.1)	135	66 (48.9)	1.00 [0.77; 1.30]; 0.979
Total[c]					1.07 [0.87; 1.31]; 0.540

(continued)

Table 15: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 3) (continued)

Outcome category Outcome Study	Tofacitinib + MTX		Adalimumab + MTX		Tofacitinib + MTX vs. adalimumab + MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Morbidity – proportion of patients with improvement					
Tender joints[d] (≤ 1)					
ORAL STANDARD	100	27 (27.0)	103	33 (32.0)	0.84 [0.55; 1.29]; 0.532
ORAL STRATEGY	106	38 (35.9)	135	50 (37.0)	0.97 [0.69; 1.36]; 0.850
Total[c]					0.91 [0.70; 1.19]; 0.509
Swollen joints[d] (≤ 1)					
ORAL STANDARD	100	42 (42.0)	103	37 (35.9)	1.17 [0.83; 1.65]; 0.529
ORAL STRATEGY	106	55 (51.9)	135	65 (48.2)	1.08 [0.84; 1.39]; 0.563
Total[c]					1.11 [0.91; 1.37]; 0.306
Fatigue (FACIT-Fatigue)[e]					
ORAL STANDARD	100	53 (53.0)	103	51 (49.5)	1.07 [0.82; 1.40]; 0.682
ORAL STRATEGY	106	56 (52.8)	135	75 (55.6)	0.95 [0.75; 1.20]; 0.675
Total[c]					1.00 [0.84; 1.20]; 0.977
Physical functioning (HAQ-DI)[f]					
ORAL STANDARD	100	56 (56.0)	103	65 (63.1)	0.89 [0.71; 1.11]; 0.326
ORAL STRATEGY	106	71 (67.0)	135	85 (63.0)	1.06 [0.88; 1.28]; 0.515
Total[c]					0.98 [0.85; 1.14]; 0.810

(continued)

Table 15: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 3) (continued)

Outcome category Outcome Study	Tofacitinib + MTX		Adalimumab + MTX		Tofacitinib + MTX vs. adalimumab + MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Side effects					
AEs (supplementary information)					
ORAL STANDARD	103	75 (72.8)	104	78 (75.0)	–
ORAL STRATEGY	106	66 (62.3)	135	89 (65.9)	–
SAEs					
ORAL STANDARD	103	17 (16.5)	104	13 (12.5)	1.32 [0.68; 2.58]; 0.531
ORAL STRATEGY	106	8 (7.6)	135	10 (7.4)	1.02 [0.42; 2.49]; 0.967
Total[c]					1.20 [0.70; 2.05]; 0.507
Discontinuation due to AEs					
ORAL STANDARD	103	13 (12.6)	104	16 (15.4)	0.82 [0.42; 1.62]; 0.682
ORAL STRATEGY	106	9 (8.5)	135	11 (8.2)	1.04 [0.45; 2.42]; 0.924
Total[c]					0.90 [0.53; 1.53]; 0.709
Infections[g]					
ORAL STANDARD	103	37 (35.9)	104	40 (38.5)	0.93 [0.66; 1.33]; 0.769
ORAL STRATEGY	106	43 (40.6)	135	54 (40.0)	1.01 [0.74; 1.38]; 0.929
Total[c]					0.98 [0.77; 1.23]; 0.849
Serious infections[h]					
ORAL STANDARD	103	8 (7.8[i])	104	3 (2.9[i])	2.69 [0.73; 9.87]; ND
ORAL STRATEGY	106	5 (4.7[i])	135	3 (2.2[i])	2.12 [0.52; 8.68]; ND
Total[c]					2.43 [0.93; 6.30]; 0.069

(continued)

Table 15: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 3) (continued)

a: At most 1 patient in the adalimumab arm, it is unclear whether death occurred in this subpopulation.
b: At most 2 patients in the tofacitinib arm, it is unclear whether the deaths occurred in this subpopulation.
c: Meta-analysis with a model with fixed effect according to Mantel-Haenzsel.
d: Based on 28 joints.
e: Patients with improvement by ≥ 4 points.
f: Patients with improvement by ≥ 0.22 points.
g: Any AEs of the SOC "infections and infestations".
h: Any SAE of the SOC "infections and infestations".
i: Institute's calculation.

ACR: American College of Rheumatology; AE: adverse event; CDAI: Clinical Disease Activity Index; CI: confidence interval; 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; RR: relative risk; SDAI: Simplified Disease Activity Index; SAE: serious adverse event; vs.: versus

Table 16: Results (morbidity and health-related quality of life, continuous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 3)

Outcome category Outcome Study	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]
Morbidity							
Pain (VAS)[d]							
ORAL STANDARD	79	60.1 (21.7)	−33.9 (30.3)	84	56.9 (19.5)	−29.4 (25.7)	−0.26 [−6.77; 6.25] 0.938
ORAL STRATEGY	85	61.3 (21.6)	−32.1 (28.6)	109	59.4 (23.0)	−28.3 (29.9)	−4.77 [−10.94; 1.41]; 0.130
Total[e]							−2.63 [−7.11; 1.85]; 0.249
Disease activity (VAS)[d]							
ORAL STANDARD	78	60.4 (21.37)	−34.5 (25.0)	84	56.3 (21.2)	−26.7 (29.4)	−5.31 [−12.10; 1.48] 0.125
ORAL STRATEGY	85	62.4 (21.7)	−36.3 (28.4)	109	60.3 (23.7)	−28.1 (31.5)	−6.91 [−13.20; −0.62] 0.031
Total[e]							−6.17 [−10.79; −1.56]; 0.009 Hedges' g −0.28 [−0.49; −0.07]
Health status (EQ-5D VAS)							
ORAL STANDARD	Outcome not recorded						
ORAL STRATEGY	No usable data						
Sleep disturbances (MOS sleep scale)							
ORAL STANDARD	No usable data						
ORAL STRATEGY	Outcome not recorded						

(continued)

Table 16: Results (morbidity and health-related quality of life, continuous) – RCT, direct comparison: tofacitinib + MTX vs. adalimumab + MTX (research question 3)(continued)

Outcome category Outcome Study	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]
Health-related quality of life							
SF-36v2 acute[f]							
Physical sum score							
ORAL STANDARD	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
ORAL STRATEGY	85	31.7 (7.15)	10.4 (8.51)	109	32.2 (7.24)	9.0 (8.07)	1.50 [−0.49; 3.49]; 0.139
Total[e]							1.08 [−0.35; 2.52]; 0.139
Mental sum score							
ORAL STANDARD	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
ORAL STRATEGY	85	39.3 (11.65)	7.1 (11.64)	109	39.9 (11.0)	4.5 (10.20)	2.58 [0.16; 5.01]; 0.036
Total[e]							1.45 [−0.31; 3.21]; 0.106

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.
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 deterioration.
e: Meta-analysis with a model with fixed effect with inverted variance.
f: Higher values indicate improvement.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions: MD: mean difference; 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

Two relevant studies were available for the assessment of the added benefit of tofacitinib. In view of the low risk of bias, at most one proof of an added benefit can be derived for the outcome “discontinuation due to AEs”. Due to the high risk of bias, at most indications of an added benefit can be derived for all other outcomes.

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 of the ORAL STANDARD study died during the observation period in the relevant study arms, namely in the adalimumab arm. During the observation period, 2 patients of the total study population of the ORAL STRATEGY study died in the tofacitinib 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

No statistically significant difference between the treatment groups was shown for the outcome "remission" for any of the operationalizations (CDAI ≤ 2.8; SDAI ≤ 3.3 and Boolean definition). 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.

Low disease activity

No statistically significant difference between the treatment groups was shown for any of the operationalizations (DAS28-4 ESR ≤ 3.2, DAS28-4 CRP ≤ 3.2, SDAI ≤ 11, CDAI ≤ 10) for the outcome "low disease activity". 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.

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.

Pain (VAS)

For the outcome "pain" (VAS), 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 this outcome; an added benefit is therefore not proven.

Disease activity (VAS)

For the outcome "disease activity" (VAS), a statistically significant difference in favour of tofacitinib + MTX was shown for the mean change. The standardized mean difference in the form of Hedges' g was considered to check the relevance of the result. The 95% CI was not completely below the irrelevance threshold of −0.2. It can therefore not be inferred that the

effect is relevant. This resulted in no hint of an added benefit of tofacitinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

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.

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.

Sleep disturbances (MOS sleep scale)

There were no usable data for the outcome "sleep disturbances" (MOS sleep scale) for the ORAL STANDARD study. This outcome was not recorded in the ORAL STRATEGY study. 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.

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, the meta-analyses showed no statistically significant differences between the treatment groups 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.

Side effects

SAEs, discontinuation due to AEs and infections

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

Further specific AEs

The company presented no complete analysis of the AEs at SOC and PT level for the relevant subpopulation for either of the two relevant studies.

Subgroups and other effect modifiers

For the ORAL STANDARD study, dossier assessment A17-18 [1] showed an effect modification relevant for the conclusion exclusively for the subgroup characteristic "age" (research question 2). For research question 3, an effect modification relevant for the conclusion was shown for none of the characteristics. Based on these results, consideration of the subgroup is restricted to the characteristic "age" in the present addendum.

For research question 3 of the ORAL STRATEGY study as well as for the ORAL STANDARD study, no statistically significant interaction between the treatment and the subgroup characteristic "age" (p-value < 0.05) was shown for any of the outcomes with usable data.

2.2.2 Probability and extent of added benefit

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 (see Table 17). 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 [5].

Table 17: Extent of added benefit at outcome level: tofacitinib + MTX vs. adalimumab + MTX (research question 3)

Outcome category **Outcome**	**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: ND[c]	Lesser benefit/added benefit not proven
Morbidity		
Remission		Lesser benefit/added benefit not proven
CDAI ≤ 2.8	Proportion: 14.0–25.5% vs. 13.6–14.1%[d] RR: 1.46 [0.96; 2.21]; p = 0.076	
SDAI ≤ 3.3	Proportion: 14.0–22.6% vs. 13.3–16.5%[d] RR: 1.26 [0.83; 1.91]; p = 0.275	
Boolean definition	Proportion: 11.0–17.9% vs. 9.7–11.9%[d] RR: 1.36 [0.83; 2.21]; p = 0.222	
Low disease activity		Lesser benefit/added benefit not proven
DAS28-4 ESR ≤ 3.2	Proportion: 18.7–29.3% vs. 25.8–28.2%[d] RR: 0.90 [0.65; 1.24]; 0.526	
DAS28-4 CRP ≤ 3.2	Proportion: 44.0–45.3% vs. 42.7–47.4%[d] RR: 0.99 [0.80; 1.21]; 0.907	
CDAI ≤ 10	Proportion: 42.0–49.1% vs. 35.9–48.9%[d] RR: 1.07 [0.87; 1.31]; 0.540	
SDAI ≤ 11	Proportion: 45.0–48.1% vs. 35.9–48.9% RR: 1.09 [0.88; 1.34]; 0.426	
Tender joints (≤ 1)	Proportion: 27.0–35.9% vs. 32.0–37.0%[e] RR: 0.91 [0.70; 1.19]; p = 0.509	Lesser benefit/added benefit not proven
Swollen joints (≤ 1)	Proportion: 42.0–51.9% vs. 35.9–48.2%[d] RR: 1.11 [0.91; 1.37]; p = 0.306	Lesser benefit/added benefit not proven
Pain (VAS)	Mean change between start of the study and month 12: −32.1 to −33.9 vs. −28.3 to −29.4[d] MD: −2.63 [−7.11; 1.85]; p = 0.249	Lesser benefit/added benefit not proven
Disease activity (VAS)	Mean change between start of the study and month 12: −34.5 to −36.3 vs. −26.7 to −28.1[d] MD: −6.17 [−10.79; −1.56]; p = 0.009 Hedges' g: −0.28 [−0.49; −0.07][e]	Lesser benefit/added benefit not proven
Fatigue (FACIT-Fatigue)[f]	Proportion: 52.8–53.0% vs. 49.5–55.6%[d] RR: 1.00 [0.84; 1.20]; p = 0.977	Lesser benefit/added benefit not proven

(continued)

Table 17: Extent of added benefit at outcome level: tofacitinib + MTX vs. adalimumab + MTX (research question 3) (continued)

Outcome category **Outcome**	**Tofacitinib + MTX vs. adalimumab + MTX** **Proportion of patients with event or change** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Morbidity (continued)		
Physical functioning (HAQ-DI)[g]	Proportion: 56.0–67.0% vs. 63.0–63.1%[d] RR: 0.98 [0.85; 1.14]; p = 0.810	Lesser benefit/added benefit not proven
Sleep disturbances (MOS sleep scale)	No usable data[h]	Lesser benefit/added benefit not proven
EQ-5D (VAS)	No usable data[i]	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: 8.1–10.4 vs. 7.6–9.0[d] MD: 1.08 [−0.35; 2.52]; p = 0.139	Lesser benefit/added benefit not proven
Mental sum score	Mean change between start of the study and month 12: 4.7–7.1 vs. 4.2–4.5[d] MD: 1.45 [−0.31; 3.21]; p = 0.106	Lesser benefit/added benefit not proven
Side effects		
SAEs	Proportion: 7.6–16.5% vs. 7.4–12.5%[d] RR: 1.20 [0.70; 2.05]; p = 0.507	Greater/lesser harm not proven
Discontinuation due to AEs	Proportion: 8.5–12.6% vs. 8.2–15.4%[d] RR: 0.90 [0.53; 1.53]; p = 0.709	Greater/lesser harm not proven
Infections	Proportion: 35.9–40.6% vs. 38.5–40.0%[d] RR: 0.98 [0.77; 1.23]; p = 0.849	Greater/lesser harm not proven
Serious Infections	Proportion: 4.7–7.8% vs. 2.2–2.9%[d] RR: 2.43 [0.93; 6.30]; p = 0.069	Greater/lesser harm not proven

(continued)

Table 17: Extent of added benefit at outcome level: tofacitinib + MTX vs. adalimumab + MTX (research question 3) (continued)

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: The company presented no analyses for the relevant subpopulation for this outcome.
d: Minimum and maximum proportions of events or mean changes in each treatment arm in the included studies.
e: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, it cannot be derived that a relevant effect is present.
f: Patients with improvement by ≥ 4 points.
g: Patients with improvement by ≥ 0.22 points.
h: For the ORAL STANDARD study, the company presented no usable data for the relevant subpopulation for this outcome, the outcome was not recorded in the ORAL STRATEGY study.
i: The outcome was not recorded in the ORAL STANDARD study, for the ORAL STRATEGY study, the company presented no usable data for the relevant subpopulation for this outcome.
ACR American College of Rheumatology; AE: adverse event; CDAI: Clinical Disease Activity Index; CI: confidence interval: upper limit of the Cl; DAS28: Disease-Activity-Score-28; EQ-5D: European Quality of Life-5 Dimensions; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; MD: mean difference; 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

Overall conclusion on added benefit

Table 18 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 18: 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.

2.2.3 List of included studies

The list of included studies was identical for research questions 2 and 3 (see Section 2.1.3).

2.3 Summary

The data subsequently submitted by the company in the commenting procedure changed the conclusion on the added benefit from dossier assessment A17-18 for research question 2

(patients with poor prognostic factors who have responded inadequately to prior treatment with 1 cDMARD): Based on the data available for the studies ORAL STANDARD and ORAL STRATEGY, there was no hint of lesser benefit for patients ≤ 65 years, an added benefit of tofacitinib in comparison with the ACT is not proven. For the other research questions, there was no change in comparison with dossier assessment A17-18 (see Table 19).

Table 19: Tofacitinib – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit[b]**
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	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**
3	Patients who have responded inadequately to prior treatment with several DMARDs (conventional DMARDs, including MTX)	bDMARD in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in 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

(continued)

Table 19: Tofacitinib – probability and extent of added benefit (continued)

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Changes in comparison with dossier assessment A17-18 are 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.
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.

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

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2. Pfizer Pharma. Tofacitinib (XELJANZ): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 21.04.2017 [Accessed: 11.08.2017]. URL: https://www.g-ba.de/informationen/nutzenbewertung/287/.

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4. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

5. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden: Version 5.0. Köln: IQWiG; 2017. URL: https://www.iqwig.de/download/Allgemeine-Methoden_Version-5-0.pdf.

Appendix A– Subgroup analyses on the outcome “SAEs”

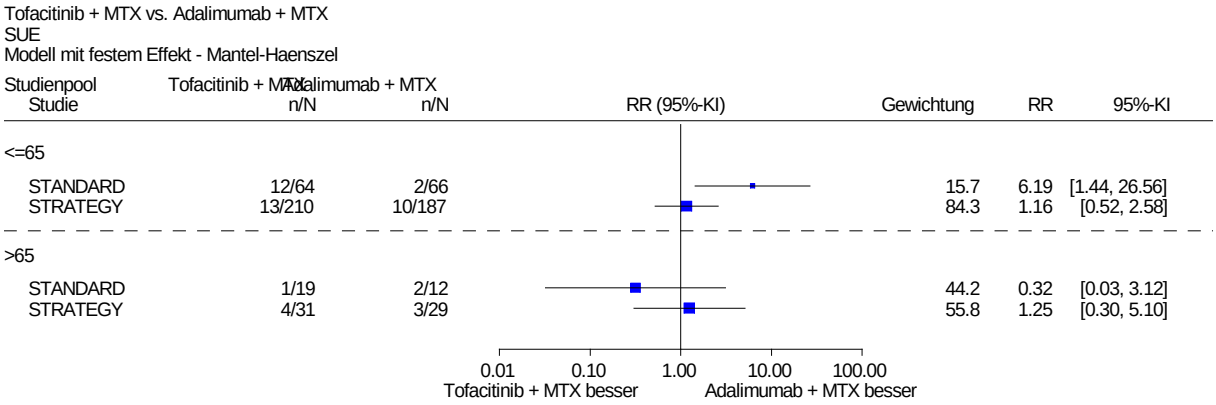

Figure 1: Data situation of the relative risks on SAEs from the studies ORAL STANDARD and ORAL STRATEGY, subgroup analyses by age (research question 2)