



IQWiG Reports – Commission No. A20-90

**Filgotinib
(rheumatoid arthritis) –
Benefit assessment according to §35a
Social Code Book V¹**

Extract

¹ Translation of Sections 2.1 to 2.6 of the dossier assessment *Filgotinib (rheumatoide Arthritis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 January 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Filgotinib (rheumatoid arthritis) – Benefit assessment according to §35a Social Code Book V

Commissioning agency

Federal Joint Committee

Commission awarded on

15 October 2020

Internal Commission No.

A20-90

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0

Fax: +49 221 35685-1

E-mail: berichte@iqwig.de

Internet: www.iqwig.de

Medical and scientific advice

- Jacqueline Detert, practice for rheumatology and immunology, Templin, Germany

IQWiG thanks the medical and scientific advisor for her contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment

- Annette Christoph
- Nadia Abu Rajab
- Katharina Biester
- Ulrich Grouven
- Simone Johner
- Florina Kerekes
- Ulrike Lampert
- Sonja Schiller

Keywords: Filgotinib, Arthritis – Rheumatoid, Benefit Assessment, NCT02889796

Table of contents

	Page
List of tables	iv
List of abbreviations	v
2 Benefit assessment	1
2.1 Executive summary of the benefit assessment	1
2.2 Research question	8
2.3 Research question 1: adult patients without poor prognostic factors and with inadequate response or intolerance to pretreatment with one csDMARD	10
2.3.1 Information retrieval and study pool	10
2.3.2 Results on added benefit.....	10
2.3.3 Probability and extent of added benefit.....	10
2.4 Research question 2: adult patients for whom a first therapy with bDMARDs or tsDMARDs is indicated	10
2.4.1 Information retrieval and study pool	10
2.4.1.1 Studies included	11
2.4.1.2 Study characteristics	11
2.4.2 Results on added benefit.....	20
2.4.2.1 Outcomes included	20
2.4.2.2 Risk of bias	23
2.4.2.3 Results.....	24
2.4.2.4 Subgroups and other effect modifiers	31
2.4.3 Probability and extent of added benefit.....	31
2.4.3.1 Assessment of the added benefit at outcome level	31
2.4.3.2 Overall conclusion on added benefit	34
2.5 Research question 3: adult patients with inadequate response or intolerance to pretreatment with one or more bDMARDs and/or tsDMARDs	35
2.5.1 Information retrieval and study pool	35
2.5.2 Results on added benefit.....	35
2.5.3 Probability and extent of added benefit.....	35
2.6 Probability and extent of added benefit – summary	35
References for English extract	37

List of tables²

	Page
Table 2: Research questions of the benefit assessment of filgotinib.....	2
Table 3: Filgotinib – probability and extent of added benefit.....	7
Table 4: Research questions of the benefit assessment of filgotinib.....	8
Table 5: Study pool – RCT, direct comparison: filgotinib + MTX vs. adalimumab + MTX ..	11
Table 6: Characteristics of the study included – RCT, direct comparison: filgotinib + MTX vs. adalimumab + MTX.....	12
Table 7: Characteristics of the intervention – RCT, direct comparison: filgotinib + MTX vs. adalimumab + MTX.....	13
Table 8: Characteristics of the study population – RCT, direct comparison: filgotinib + MTX vs. adalimumab + MTX.....	17
Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: filgotinib + MTX vs. adalimumab + MTX.....	19
Table 10: Matrix of outcomes – RCT, direct comparison: filgotinib + MTX vs. adalimumab + MTX	21
Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: filgotinib + MTX vs. adalimumab + MTX.....	23
Table 12: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: filgotinib + MTX vs. adalimumab + MTX.....	25
Table 13: Results (morbidity and health-related quality of life, continuous) – RCT, direct comparison: filgotinib + MTX vs. adalimumab + MTX.....	27
Table 14: Extent of added benefit at outcome level: filgotinib + MTX vs. adalimumab + MTX	32
Table 15: Positive and negative effects from the assessment of filgotinib + MTX in comparison with adalimumab + MTX.....	34
Table 16: Filgotinib – probability and extent of added benefit.....	36

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

List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ACT	appropriate comparator therapy
AE	adverse event
bDMARD	biologic DMARD
CCP	cyclic citrullinated peptide
CDAI	Clinical Disease Activity Index
CI	confidence interval
CrCl	creatinine clearance
CRP	C-reactive protein
csDMARD	conventional synthetic DMARD
DAS28	Disease Activity Score based on 28 joints
DMARD	disease-modifying antirheumatic drug
EQ-5D	European Quality of Life-5 Dimensions
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
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)
JAK	Janus kinase
MMRM	mixed-effects model with repeated measures
MTX	methotrexate
NRI	non-responder imputation
RCT	randomized controlled trial
SAE	serious adverse event
SDAI	Simplified Disease Activity Index
SF-36	Short Form 36 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product characteristics
TNF	tumour necrosis factor
tsDMARD	targeted synthetic DMARD
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug filgotinib. 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 15 October 2020.

Research question

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

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

Table 2: Research questions of the benefit assessment of filgotinib

Research question	Therapeutic indication	ACT ^a
Adults with moderate to severe active rheumatoid arthritis		
1	Patients without poor prognostic factors ^b who have responded inadequately to, or who have not tolerated prior treatment with one disease-modifying antirheumatic drug (csDMARD ^c , including methotrexate [MTX])	Alternative csDMARDs ^c if suitable (e.g. MTX, leflunomide) as monotherapy or combination therapy
2	Patients for whom a first therapy with bDMARDs or tsDMARDs is indicated ^d	bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability)
3	Patients who have responded inadequately to, or who have not tolerated prior treatment with one or more bDMARDs and/or tsDMARDs	Switching of bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability; or, in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on prior therapy ^e
<p>a. Presentation of the respective ACT specified by the G-BA. b. Poor prognostic factors: detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antigen antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions. c. In the G-BA's specification of the ACT, csDMARDs are referred to as "classical DMARDs". The present benefit assessment uses the term "csDMARDs". d. This comprises both patients with poor prognostic factors who have responded inadequately to, or who have not tolerated prior treatment with one csDMARD (including MTX), and patients who have responded inadequately to or have not tolerated prior treatment with several csDMARDs (including MTX). e. Switching the mode of action should be considered depending on the prior therapy.</p> <p>ACT: appropriate comparator therapy; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate; tsDMARD: targeted synthetic DMARD</p>		

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

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

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

The company followed the G-BA's specification of the ACT without taking into account the option of infliximab. This had no consequence for the present benefit assessment.

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.

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

The company presented no data for the assessment of the added benefit of filgotinib in comparison with the ACT for adult patients without poor prognostic factors who have responded inadequately to, or who have not tolerated prior treatment with one csDMARD. This resulted in no hint of an added benefit of filgotinib in comparison with the ACT. An added benefit is therefore not proven.

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

Study pool and study characteristics

The study pool of the benefit assessment of filgotinib in comparison with the ACT for research question 2 consists of the RCT FINCH 1, which compared filgotinib + MTX with filgotinib + MTX. The study is exclusively suitable for deriving conclusions on the added benefit of filgotinib for the combination therapy with MTX.

The FINCH 1 study is a 4-arm, randomized, double-blind study on the comparison of filgotinib in 2 dosages with adalimumab and placebo, each in combination with MTX. The study included adult patients with moderate to severe active rheumatoid arthritis who have an inadequate response to MTX treatment. The patients had to have received continuous treatment with MTX at stable dosing for ≥ 12 weeks and had to continue this dosage as concomitant treatment during the study.

A total of 1759 patients were randomly allocated to the 4 treatment arms of filgotinib 200 mg + MTX (N = 477), filgotinib 100 mg + MTX (N = 480), adalimumab + MTX (N = 325) and placebo + MTX (N = 477). Besides the comparator arm of adalimumab + MTX, the study arm of filgotinib 200 mg + MTX is relevant for the present benefit assessment.

For the majority of the patients, treatment with filgotinib and adalimumab was in compliance with the recommendations of the respective Summary of Product Characteristics (SPC). However, for an unknown proportion of patients, treatment in the study arm with filgotinib 200 mg was not in compliance with the approval (concomitant treatment with another csDMARD, no dose adjustment for patients with renal function disorder or aged > 75 years).

The planned double-blind, randomized treatment phase was 52 weeks. After the end of the study, patients in the filgotinib study arms could continue their therapy in an open-label long-term extension study.

The primary outcome of the study was defined as the proportion of patients with a 20% improvement in American College of Rheumatology (ACR) criteria at week 12 in comparison with placebo. Patient-relevant outcomes on morbidity, health-related quality of life and AEs were additionally recorded.

In the FINCH 1 study, therapy adjustments were made at predefined time points at week 14 and starting from week 30 if certain criteria for response to treatment were not met. Patients continued treatment in accordance with local standards of care and the investigator's decision. The study visits and examinations were to be continued until the end of the study.

The present benefit assessment is based on the final analysis of the FINCH 1 study (week 52). At this time point, 83.8% of the patients were still being treated with filgotinib 200 mg + MTX and 81.8% with adalimumab + MTX.

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes was rated as low for the FINCH 1 study. The outcome-specific risk of bias was rated as low for the results of the categories of all-cause mortality, health-related quality of life, for all outcomes of the category of side effects, and for the morbidity outcomes of tender and swollen joints, and as high for the results for all other morbidity outcomes. The reason for the high risk of bias is a high proportion of patients who were rated as non-responders due to missing values or discontinuation of the study medication.

It is unclear how many patients in the FINCH 1 study were not treated in compliance with the approval. These uncertainties lead overall to a reduced certainty of conclusions. On the basis of the effects shown in the FINCH 1 study, at most hints, e.g. of an added benefit, can therefore be derived for all outcomes.

Results

Mortality

All-cause mortality

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of filgotinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

Morbidity

Clinical remission (Clinical Disease Activity Index [CDAI])

A statistically significant difference in favour of filgotinib + MTX was shown for the outcome "clinical remission" based on the $CDAI \leq 2.8$. The sensitivity analyses using alternative imputation strategies did not confirm this effect regarding statistical significance, however. This

resulted in a hint of an added benefit of filgotinib + MTX in comparison with adalimumab + MTX.

Low disease activity (CDAI)

No statistically significant difference between the treatment groups was shown for the outcome “low disease activity” on the basis of the $CDAI \leq 10$. This resulted in no hint of an added benefit of filgotinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

Tender and swollen joints

A statistically significant difference in favour of filgotinib + MTX was shown for each of the outcomes “tender joints” and “swollen joints” based on the mean differences. The corresponding 95% confidence interval (CI) of the mean change included a difference of < 1 joint in each case. It can therefore not be inferred that the effect was relevant. This resulted in no hint of an added benefit of filgotinib + MTX in comparison with adalimumab + MTX in each case; an added benefit is therefore not proven for these outcomes.

Pain (visual analogue scale [VAS]), patient assessment of disease activity (VAS), health status (European Quality of Life-5 Dimensions [EQ-5D] VAS)

For the outcomes “pain” (VAS), “patient assessment of disease activity” (VAS) and “health status” (EQ-5D VAS), there was no statistically significant difference between the treatment groups based on the responder analyses with an improvement of ≥ 15 points. This resulted in no hint of an added benefit of filgotinib + MTX in comparison with adalimumab + MTX for each of these outcomes; an added benefit is therefore not proven in each case.

Physical functioning (Health Assessment Questionnaire-Disability Index [HAQ-DI]) and fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-Fatigue])

For the outcomes “physical functioning” (HAQ-DI) and “fatigue” (FACIT-Fatigue), there was no statistically significant difference between the treatment groups based on the responder analyses with an improvement of ≥ 0.45 points or ≥ 7.8 points. This resulted in no hint of an added benefit of filgotinib + MTX in comparison with adalimumab + MTX in each case; an added benefit is therefore not proven for these outcomes.

Health-related quality of life

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

For the Physical and the Mental Component Summary of the SF-36, there was no statistically significant difference between the treatment groups on the basis of the continuous analyses. In each case, this resulted in no hint of an added benefit of filgotinib + MTX in comparison with adalimumab + MTX.

Side effects

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

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

Probability and extent of added benefit, patient groups with therapeutically important added benefit³

Based on the results presented, probability and extent of the added benefit of the drug filgotinib in comparison with the ACT are assessed as follows:

Overall, there is exclusively one positive effect of filgotinib + MTX in comparison with adalimumab + MTX for adult patients for whom a first therapy with bDMARDs or tsDMARDs is indicated (outcome “clinical remission”). This positive effect is not accompanied by negative effects.

In summary, there is a hint of a minor added benefit of filgotinib + MTX in comparison with the ACT for patients with moderate rheumatoid arthritis for whom a first therapy with bDMARDs or tsDMARDs is indicated and who have normal renal function or mild renal function disorder (creatinine clearance [CrCl] \geq 60 mL/min).

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

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

The company presented no data for the assessment of the added benefit of filgotinib in adult patients who have responded inadequately to, or who have not tolerated prior treatment with one or more bDMARDs and/or tsDMARDs. An added benefit of filgotinib in comparison with the ACT is therefore not proven for these patients.

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

Probability and extent of added benefit – summary

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

Table 3: Filgotinib – probability and extent of added benefit

Subindication	ACT ^a	Probability and extent of added benefit
Adults with moderate to severe active rheumatoid arthritis		
Patients without poor prognostic factors ^b who have responded inadequately to, or who have not tolerated prior treatment with one disease-modifying antirheumatic drug (csDMARD ^c , including methotrexate [MTX])	Alternative csDMARDs ^c if suitable (e.g. MTX, leflunomide) as monotherapy or combination therapy	Added benefit not proven
Patients for whom a first therapy with bDMARDs or tsDMARDs is indicated ^d	bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability)	Combination with MTX: ▪ hint of minor added benefit ^e
		Monotherapy: added benefit not proven
Patients who have responded inadequately to, or who have not tolerated prior treatment with one or more bDMARDs and/or tsDMARDs	Switching of bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability; or, in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on prior therapy ^f	Added benefit not proven
<p>a. Presentation of the respective ACT specified by the G-BA.</p> <p>b. Poor prognostic factors: detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antigen antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.</p> <p>c. In the G-BA's specification of the ACT, csDMARDs are referred to as "classical DMARDs". The present benefit assessment uses the term "csDMARDs".</p> <p>d. This comprises both patients with poor prognostic factors who have responded inadequately to, or who have not tolerated prior treatment with one csDMARD (including MTX), and patients who have responded inadequately to or have not tolerated prior treatment with several csDMARDs (including MTX).</p> <p>e. The added benefit relates exclusively to patients with normal renal function or mild renal function disorder (CrCl ≥ 60 mL/min).</p> <p>f. Switching the mode of action should be considered depending on the prior therapy.</p> <p>ACT: appropriate comparator therapy; bDMARD: biologic DMARD; CrCl: creatinine clearance; csDMARD: conventional synthetic DMARD; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate; tsDMARD: targeted synthetic DMARD</p>		

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of filgotinib as monotherapy or in combination with MTX in comparison with the ACT in adult patients with moderate to severe active rheumatoid arthritis who have responded inadequately to, or who are intolerant to one or more DMARDs.

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

Table 4: Research questions of the benefit assessment of filgotinib

Research question	Subindication	ACT ^a
Adults with moderate to severe active rheumatoid arthritis		
1	Patients without poor prognostic factors ^b who have responded inadequately to, or who have not tolerated prior treatment with one disease-modifying antirheumatic drug (csDMARD ^c , including methotrexate [MTX])	Alternative csDMARDs ^c if suitable (e.g. MTX, leflunomide) as monotherapy or combination therapy
2	Patients for whom a first therapy with bDMARDs or tsDMARDs is indicated ^d	bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability)
3	Patients who have responded inadequately to, or who have not tolerated prior treatment with one or more bDMARDs and/or tsDMARDs	Switching of bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability; or, in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on prior therapy ^e
<p>a. Presentation of the respective ACT specified by the G-BA.</p> <p>b. Poor prognostic factors: detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antigen antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.</p> <p>c. In the G-BA's specification of the ACT, csDMARDs are referred to as "classical DMARDs". The present benefit assessment uses the term "csDMARDs".</p> <p>d. This comprises both patients with poor prognostic factors who have responded inadequately to, or who have not tolerated prior treatment with one csDMARD (including MTX), and patients who have responded inadequately to or have not tolerated prior treatment with several csDMARDs (including MTX).</p> <p>e. Switching the mode of action should be considered depending on the prior therapy.</p> <p>ACT: appropriate comparator therapy; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate; tsDMARD: targeted synthetic DMARD</p>		

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

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

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

With the resolution on upadacitinib (16 July 2020), the G-BA expanded the ACT of research questions 2 and 3 to include infliximab as an additional tumour necrosis factor (TNF) α inhibitor. The company followed the G-BA's original determination of the ACT without making a choice. The fact that infliximab was not considered had no consequence for the present benefit assessment, as this did not call into question the completeness of the study pool presented by the company.

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

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

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on filgotinib (status: 3 August 2020)
- bibliographical literature search on filgotinib (last search on 3 August 2020)
- search in trial registries/trial results databases for studies on filgotinib (last search on 5 August 2020)
- search on the G-BA website for filgotinib (last search on 5 August 2020)

To check the completeness of the study pool:

- search in trial registries for studies on filgotinib (last search on 20 October 2020)

The company presented no study for research question 1. No relevant study was identified from the check either.

2.3.2 Results on added benefit

The company presented no data for the assessment of the added benefit of filgotinib in comparison with the ACT for adult patients without poor prognostic factors who have responded inadequately to, or who have not tolerated prior treatment with one csDMARD. This resulted in no hint of an added benefit of filgotinib in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

The company presented no data for the assessment of the added benefit of filgotinib in adult patients without poor prognostic factors who have responded inadequately to, or who have not tolerated prior treatment with one csDMARD. An added benefit of filgotinib in comparison with the ACT is therefore not proven for these patients.

This concurs with the assessment of the company, which claimed no added benefit for this patient group.

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

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on filgotinib (status: 3 August 2020)
- bibliographical literature search on filgotinib (last search on 3 August 2020)
- search in trial registries/trial results databases for studies on filgotinib (last search on 5 August 2020)
- search on the G-BA website for filgotinib (last search on 5 August 2020)

To check the completeness of the study pool:

- search in trial registries for studies on filgotinib (last search on 20 October 2020)

The check did not identify any additional relevant studies.

2.4.1.1 Studies included

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

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

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study ^a (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries ^b (yes/no [citation])	Publication (yes/no [citation])
GS-US-417-0301 (FINCH 1 ^c)	Yes	Yes	No	No ^d	Yes [3,4]	No

a. Study for which the company was sponsor.
 b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
 c. In the following tables, the study is referred to with this abbreviated form.
 d. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.
 CSR: clinical study report; RCT: randomized controlled trial; vs.: versus

The study pool of the benefit assessment of filgotinib in comparison with the ACT for research question 2 consisted of the RCT FINCH 1 and corresponded to the study pool of the company. The study compared filgotinib + MTX with adalimumab + MTX. The study FINCH 1 is exclusively suitable for deriving conclusions on the added benefit of filgotinib for the combination therapy with MTX.

2.4.1.2 Study characteristics

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
FINCH 1	RCT, double-blind, parallel	Adult patients with moderate to severe rheumatoid arthritis ^b <ul style="list-style-type: none"> ▪ with inadequate response to MTX ▪ with continuous treatment with MTX for ≥ 12 weeks and on a stable dose ≥ 4 weeks before first dose of study medication (7.5–25 mg per week) 	Filgotinib 200 mg + MTX (N = 477) filgotinib 100 mg + MTX (N = 480) ^{c, d} adalimumab + MTX (N = 325) placebo + MTX (N = 477) ^{d, e}	Screening: ND Treatment: 52 weeks ^f Observation: 30 days ^g	303 centres in: Argentina, Australia, Belgium, Bulgaria, Canada, Czech Republic, Germany, Hong Kong, Hungary, India, Ireland, Israel, Italy, Japan, Mexico, Netherlands, New Zealand, Poland, Republic of Korea, Romania, Russia, Serbia, Slovakia, South Africa, Spain, Taiwan, Thailand, Ukraine, United Kingdom, USA 8/2016–6/2019 Data cut-off at week 24: 8 Oct 2018 Data cut-off at week 52: 20 Jun 2019	Primary: ACR20 at week 12 Secondary: morbidity, health-related quality of life, AEs
<p>a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.</p> <p>b. Diagnosed according to 2010 ACR/EULAR classification criteria with ACR classes I to III.</p> <p>c. This dosage is approved for patients with moderate or severe renal function disorder (CrCl 15 to < 60 mL/min). In the FINCH 1 study, only very few patients with moderate or severe renal function disorder were included (see also Section 2.4.3.2).</p> <p>d. The arm is not relevant for the assessment and is no longer presented in the following tables.</p> <p>e. As of week 24, all patients in the placebo arm were re-randomized to one of the 2 filgotinib dosages.</p> <p>f. Patients who had not reached a $\geq 20\%$ improvement from baseline in SJC and TJC for 2 consecutive visits at week 14 or starting from week 30, respectively, had to discontinue study treatment and receive standard therapy at the investigator's discretion. Study visits and assessments were to be continued according to protocol.</p> <p>g. Follow-up observation of AEs; patients in the treatment arms with filgotinib who did not discontinue the study medication and showed sufficient response had the opportunity to participate in a long-term extension study afterwards.</p> <p>ACR: American College of Rheumatology; ACR20: 20% improvement in ACR criteria; AE: adverse event; CrCl: creatinine clearance; EULAR: European League Against Rheumatism; MTX: methotrexate; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SJC: swollen joint count; TJC: tender joint count; vs.: versus</p>						

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

Study	Intervention	Comparison
FINCH 1	Filgotinib 200 mg/day, orally + placebo in each case corresponding to the other treatment arms	Adalimumab 40 mg SC, every 2 weeks
<p>Allowed prior and concomitant treatment</p> <ul style="list-style-type: none"> ▪ MTX: continuation of the oral therapy maintained for ≥ 12 weeks, of which ≥ 4 weeks on a stable dose (7.5–25 mg per week) before first dose of study medication; in case of intolerance of higher dosages: stable dose of < 7.5 mg/week ▪ folic acid supplementation (≥ 5 mg/week or in accordance with local clinical practice) ▪ hydroxychloroquine ≤ 400 mg/day or chloroquine ≤ 250 mg/day allowed if dosing had been stable for ≥ 4 weeks before first dose of study medication ▪ NSAIDs on a stable dose ≥ 2 weeks before first dose of study medication ▪ oral corticosteroids (prednisone ≤ 10 mg/day or equivalent) or on a stable dose > 4 weeks before first dose of study medication <p>Prohibited prior and concomitant treatment</p> <ul style="list-style-type: none"> ▪ JAK inhibitors ▪ bDMARDs with inadequate response or treatment duration ≥ 3 months^a ▪ adalimumab ▪ rituximab ▪ leflunomide^b ▪ hydroxychloroquine or chloroquine if discontinued < 4 weeks before first dose of study medication, sulfasalazine^c ▪ alkylating drugs such as chlorambucil or cyclophosphamide ▪ live vaccines^d ▪ surgical treatment of RA (including synovectomy or endoprosthetics in > 4 joints) ▪ current therapy for chronic infections ▪ IA or parenteral corticosteroids^e ▪ other drugs such as ciclosporin, other calcineurin inhibitors, gold therapy, mycophenolate mofetil, or azathioprine^e 		
<p>a. Treatment < 3 months, in a maximum of 20% of the total study population was allowed. b. ≤ 8 weeks before first dose of study medication or in case of washout with cholestyramine < 4 weeks before first dose of study medication. c. Within 4 weeks after the first visit. d. ≤ 30 days before first dose of study medication or as planned treatment during the study. e. Within 4 weeks before first dose of study medication.</p> <p>bDMARD: biologic DMARD; DMARD: disease-modifying antirheumatic drug; IA: intraarticular; JAK: Janus kinase; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; RA: rheumatoid arthritis; RCT: randomized controlled; SC: subcutaneous; vs.: versus</p>		

The FINCH 1 study is a 4-arm, randomized, double-blind study on the comparison of filgotinib in 2 dosages with adalimumab and placebo, each in combination with MTX.

The study included adult patients with moderate to severe active rheumatoid arthritis who have an inadequate response to MTX treatment. Diagnosis of rheumatoid arthritis had to be conducted according to the 2010 ACR/European League Against Rheumatism (EULAR)

classification criteria [5] and had to be consistent with ACR classes I to III. In addition, patients had to fulfil the following criteria to be eligible for enrolment:

- ≥ 6 swollen and ≥ 6 tender joints, based on 66 or 68 joint counts respectively
- either ≥ 1 documented joint erosion and a positive cyclic citrullinated peptide (CCP) antibody test, or a positive rheumatoid factor test, or ≥ 3 documented joint erosions if both tests are negative or a C-reactive protein (CRP) level of ≥ 6 mg/L

For ≥ 12 weeks before the start of treatment with the study medication, the patients had to have received continuous treatment with MTX, which had to be on a stable dose within the last 4 weeks before the first dose of the study medication. This dosage was continued as concomitant treatment during the study.

A total of 1759 patients were randomly allocated in a 3:3:2:3 ratio to the 4 treatment arms of filgotinib 200 mg + MTX (N = 477), filgotinib 100 mg + MTX (N = 480), adalimumab + MTX (N = 325) and placebo + MTX (N = 477). The characteristics of region, prior bDMARD therapy (yes/no), and the presence of rheumatoid factor or anti-CCP antibodies were used for stratification.

Besides the comparator arm of adalimumab + MTX, the study arm of filgotinib 200 mg + MTX is relevant for the present benefit assessment because this is the approved dosage of filgotinib. This does not include the treatment of patients with moderate or severe renal function disorder, for whom a dosage of 100 mg filgotinib has been approved. The latter is also the recommended starting dose for patients > 75 years of age. The following description refers exclusively to the study arms of filgotinib 200 mg + MTX and adalimumab + MTX, as the majority of patients included in the study are those for whom 200 mg filgotinib is the approved dosage.

For the majority of the patients, treatment with filgotinib and adalimumab was in compliance with the recommendations of the SPCs [6,7] (see also Section on limitations of the study).

The planned double-blind, randomized treatment phase was 52 weeks. After the end of the study, patients in the filgotinib study arms could continue their therapy in an open-label long-term extension study.

The primary outcome of the study was defined as the proportion of patients with a 20% improvement in ACR criteria at week 12 in comparison with placebo. Patient-relevant outcomes on morbidity, health-related quality of life and AEs were additionally recorded.

In the FINCH 1 study, therapy adjustments were made at predefined time points if certain criteria for response to treatment were not met. At week 14, patients with $< 20\%$ improvement in swollen and tender joint count in comparison with the start of treatment had to discontinue the study treatment. They continued treatment in accordance with local standards of care and the investigator's decision. According to the protocol, the study visits and examinations were to be continued until the end of the study. The same measures applied to patients who achieved

< 20% improvement in swollen and tender joint count in comparison with the start of treatment on 2 consecutive visits from week 30 onwards. It is unclear whether the count was based on the assessment of 66 swollen and 68 tender joints or of 28 joints each. Module 4 A of the dossier does not contain any information on the type of therapy used for the continued treatment of the patients after discontinuation of the study medication.

For the FINCH 1 study, analyses are available for week 12, week 24 and week 52. The company used the final analyses at week 52 for the outcomes it presented. At this time point, 83.8% of the patients were still being treated with filgotinib 200 mg + MTX and 81.8% with adalimumab + MTX. In accordance with the company's approach, the present benefit assessment is based on the final analysis at week 52.

Patients with renal function disorder

A dosage of 100 mg filgotinib once daily is approved for patients with moderate or severe renal function disorder (CrCl 15 to < 60 mL/min) [6]. Such a dose reduction was not mandated for these patients in the study arm of filgotinib 200 mg; in the study arm of filgotinib 100 mg + MTX, the treatment of this patient group was in compliance with the approval. The proportion of patients with such renal function disorder was very small, however (n = 23 in the filgotinib 100 mg + MTX arm, n = 12 in the adalimumab + MTX arm). The company presented descriptive analyses of this subpopulation in the Appendix of Module 4 A, but did not prepare the data. It presented neither effect estimations nor CIs for the analyses and did not include these data in the derivation of the added benefit in the present therapeutic indication (see also Section 2.4.3.2). These data are therefore also not the subject of the present benefit assessment.

Limitations of the study

For an overall unknown proportion of patients, treatment in the study arm of filgotinib 200 mg + MTX did not comply with the approval:

- **Combination of filgotinib with MTX and other csDMARDs:** According to the inclusion criteria, concomitant treatment with the csDMARDs hydroxychloroquine \leq 400 mg/day or chloroquine \leq 250 mg/day was allowed during the study if this treatment had been administered at a stable dosage for \geq 4 weeks before the first dose of the study medication. Concomitant treatment with other csDMARDs in addition to MTX does not comply with the recommendations of the SPCs of filgotinib [6] or adalimumab [7], however. The company did not provide any information in Module 4 A on how many of the patients in the study arms relevant for the benefit assessment received such additional concomitant treatment.

In the Appendix of Module 4 A, the company presented patient characteristics of a small subpopulation of patients with moderate or severe renal function disorder from the FINCH 1 study for the treatment arms of filgotinib 100 mg and adalimumab, each in combination with MTX (see above). These data show that in this population the proportion of patients with additional treatment with (hydroxy)chloroquine was < 20%.

Even though this conclusion was only based on a small number of patients, it is assumed, due to the randomization, that the proportion of patients in the study population considered for the benefit assessment is of a similar magnitude.

- Age > 75 years: The starting dose of 100 mg daily approved for patients > 75 years according to the SPC of filgotinib was not taken into account. Although there is no information in Module 4 A on how many patients this applies to, it can be estimated on the basis of the available information on the age of the patients that the proportion of > 75-year-olds was < 5%.
- Moderate or severe renal function disorder: Patients with moderate or severe renal function disorder (CrCl 15 to < 60 mL/min) randomized to the treatment arm of filgotinib 200 mg + MTX were not treated with the filgotinib dose of 100 mg approved in the SPC. According to Module 4 A, 3.7% of the patients in the adalimumab arm had such renal function disorder.

The company did not base the derivation of the added benefit on a definition of the relevant subpopulation for research question 2, but on the total population of the FINCH 1 study. It is unclear which proportion of patients receiving treatment that was not in compliance with the approval was overall included in the study population and whether this proportion accounts for > 20% of the study population. This uncertainty did not lead to the exclusion of the study from the benefit assessment. It is assumed that conclusions on the added benefit of filgotinib (in combination with MTX) can be derived on the basis of this study. The uncertainty is taken into account in the certainty of conclusions (see Section 2.4.2.2).

Characteristics of the study population

Table 8 shows the characteristics of the patients in the study included.

Table 8: Characteristics of the study population – RCT, direct comparison: filgotinib + MTX vs. adalimumab + MTX (multipage table)

Study Characteristic Category	Filgotinib + MTX N ^a = 477	Adalimumab + MTX N ^a = 325
FINCH 1		
Age [years], mean (SD)	52 (13)	53 (13)
Sex [F/M], %	80/20	82/18
Region, n (%)		
Group A ^b	108 (23)	73 (23)
Group B ^c	259 (55)	175 (54)
Group C ^d	48 (10)	35 (11)
Group D ^e	20 (4)	14 (4)
Group E ^f	40 (8)	28 (9)
Disease duration: time between first diagnosis and randomization [years], mean (SD)	7.3 (7.4)	8.0 (7.4)
Rheumatoid factor, n (%)		
Yes	352 (74)	241 (74)
No	123 (26)	84 (26)
Anti-CCP, n (%)		
Yes	380 (80)	253 (78)
No	95 (20)	70 (22)
Missing	0 (0)	2 (1)
DAS28 (CRP), (disease activity at baseline), mean (SD)	5.8 (0.9)	5.7 (0.9)
DAS28 (CRP), (disease activity at baseline), n (%)		
≤ 5.1	106 (22)	74 (23)
> 5.1	369 (78)	251 (77)
Tender joint count ^g , mean (SD)	15 (6.4)	15 (6.3)
Swollen joint count ^g , mean (SD)	11 (5.2)	11 (5.0)
Functional status [HAQ-DI], mean (SD)	1.59 (0.6)	1.59 (0.6)
bDMARDs – pretreatment, n (%)		
Yes	17 (4)	8 (3)
No	458 (96)	317 (98)
Glucocorticoid therapy at start of therapy		
Yes	229 (48)	140 (43)
Dose [mg/week], mean (SD)	6.2 (3.4) ^h	5.9 (2.2)
No	246 (52)	185 (57)
Treatment discontinuation, n (%)	77 (16.2) ⁱ	59 (18.2) ⁱ
Study discontinuation, n (%)	51 (10.7) ⁱ	44 (13.5) ⁱ

Table 8: Characteristics of the study population – RCT, direct comparison: filgotinib + MTX vs. adalimumab + MTX (multipage table)

Study Characteristic Category	Filgotinib + MTX N ^a = 477	Adalimumab + MTX N ^a = 325
<p>a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.</p> <p>b. USA, South Africa, Republic of Korea, Spain, Germany, New Zealand, Great Britain, Canada, Israel, Belgium, Italy, Netherlands, Australia and Ireland.</p> <p>c. Poland, Ukraine, India, Russia, Hungary, Bulgaria, Czech Republic, Romania, Serbia and Slovak Republic.</p> <p>d. Mexico and Argentina.</p> <p>e. Taiwan, Thailand and Hong Kong.</p> <p>f. Japan.</p> <p>g. Based on 28 joints.</p> <p>h. No data for 2 patients.</p> <p>i. Institute's calculation.</p> <p>bDMARD: biologic DMARD; CCP: cyclic citrullinated peptide; CRP: C-reactive protein; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; DMARD: disease-modifying antirheumatic drug; F: female; HAQ-DI: Health Assessment Questionnaire-Disability Index; M: male; MTX: methotrexate; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs: versus</p>		

The demographic and clinical characteristics between the 2 arms of the FINCH 1 study were sufficiently balanced. The mean age of the patients was 52 and 53 years, and most of them were women (about 80%). About 3 quarters of the patients had high disease activity at baseline (defined as Disease Activity Score based on 28 joints [DAS28] [CRP] > 5.1). Up to 80% of the patients had poor prognostic factors, such as a positive rheumatoid factor or anti-CCP antibody status. Less than 5% of the study population had received pretreatment with bDMARDs for < 3 months. Thus, the vast majority of the study population concurred with the population relevant for this research question, i.e. adult patients for whom a first therapy with bDMARDs or tsDMARDs is indicated. Limitations regarding the relevant study population arising from the requirements of the SPC of filgotinib are described above in the section on limitations of the study.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: filgotinib + 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
			Patients	Treating staff			
FINCH 1	Yes	Yes	Yes	Yes	Yes	Yes	Low

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

The risk of bias across outcomes was rated as low for the FINCH 1 study. This concurs with the company’s assessment.

Transferability of the study results to the German health care context

The company described in Module 4 A that the results of the FINCH 1 study are assumed to be transferable to the German health care context. One of the reasons given by the company for this is that almost 70% the study population of the FINCH 1 study were white patients. Due to the structural similarity between the study participants and the target population in the therapeutic indication, especially with regard to the clinical parameters, the company assumed that the clinical effects observed in the FINCH 1 study also occur in health care under everyday conditions. In addition, according to the company, the subgroup analyses conducted in the FINCH 1 study had not shown any effect modification by the factor of geographical region.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
 - all-cause mortality
- Morbidity
 - clinical remission
 - low disease activity
 - tender joints
 - swollen joints
 - pain (recorded using a VAS)
 - patient assessment of disease activity (recorded using a VAS)
 - physical functioning (recorded using the HAQ-DI)
 - fatigue (recorded using the FACIT-Fatigue)
 - health status (recorded using the EQ-5D VAS)
- Health-related quality of life
 - recorded using the Physical and Mental Component Summary of the SF-36
- Side effects
 - SAEs
 - discontinuation due to AEs
 - infections (System Organ Class [SOC] “infections and infestations”, AEs)
 - serious infections (SOC “infections and infestations”, SAEs)
 - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes of the category of side effects in the dossier (Module 4 A).

Table 10 shows for which outcomes data were available in the study included.

Table 10: Matrix of outcomes – RCT, direct comparison: filgotinib + MTX vs. adalimumab + MTX

Study	Outcomes														
	All-cause mortality	Clinical remission (CDAI \leq 2.8) ^a	Low disease activity (CDAI \leq 10) ^b	Tender joints ^c	Swollen joints ^c	Pain (VAS)	Patient assessment of disease activity (VAS)	Physical functioning (HAQ-DI)	Fatigue (FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Infections (SOC, AE) ^d	Serious infections (SOC, SAE) ^d
FINCH 1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
a. Supplementary presentation: SDAI \leq 3.3 and Boolean definition, see Appendix B of the full dossier assessment. b. Supplementary presentation: SDAI \leq 11 and DAS28 (CRP) \leq 3.2, see Appendix B of the full dossier assessment. c. Based on 28 joints. d. All AEs of the MedDRA SOC “infections and infestations” are used for the recording of infections, and all SAEs for the recording of serious infections. AE: adverse event; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: Disease Activity Score based on 28 joints; EQ-5D: European Quality of Life-5 Dimensions; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; MedDRA: Medical Dictionary for Regulatory Activities; MTX: methotrexate; RCT: randomized controlled trial; SAE: serious adverse event; SDAI: Simplified Disease Activity Index; SF-36: Short Form 36 Health Survey; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus															

Morbidity – clinical remission and low disease activity

In the present benefit assessment, the assessment of the outcomes “clinical remission” and “low disease activity” is based on the CDAI. In contrast to the other definitions provided by the company (Simplified Disease Activity Index [SDAI] or Boolean definition), the calculation of clinical remission/low disease activity on the basis of the CDAI does not include the recording of inflammatory markers. This allows a fair assessment of drugs that have an enhanced effect on lowering inflammatory markers in the blood in comparison with those that do not. According to the current EULAR guideline, it is explicitly recommended for Janus kinase (JAK) inhibitors that the choice of a suitable instrument for the recording of disease activity should take into account their direct effects on inflammatory markers [8].

In fact, the FINCH 1 study showed discrepant results for the operationalization of low disease activity using the SDAI compared with the CDAI. This could be due to the inflammatory component in the SDAI. The results of the operationalizations “SDAI” and “Boolean

definition” are presented in Appendix B of the full report together with the presentation of the operationalization “DAS28”.

Morbidity – symptoms and health-related quality of life

The company presented several operationalizations and types of analyses in Module 4 A for the outcomes on symptoms and health-related quality of life.

- For the derivation of the added benefit for the outcomes “physical functioning” (HAQ-DI), “fatigue” (FACIT-Fatigue) and “health-related quality of life” (SF-36), the company used responder analyses for the proportion of patients with an improvement of ≥ 0.22 points (HAQ-DI), ≥ 4 points (FACIT-Fatigue) and ≥ 5 points (SF-36).
- For the outcomes “patient assessment of disease activity”, “pain” and “health status” (EQ-5D), which are all assessed with a VAS, the company used continuous analyses based on a mixed-effects model with repeated measures (MMRM model) to derive the added benefit. It also presented such continuous analyses for all other outcomes on symptoms and health-related quality of life as supplementary information.
- Following IQWiG’s draft methods, the company additionally presented analyses with a response criterion of 15% of the scale range for all patient-reported outcomes in the Appendix of Module 4 A, but did not use these to derive the added benefit (these are HAQ-DI: 0.45 points; FACIT-Fatigue: 7.8 points; VAS-based outcomes and SF-36: 15 mm and 15 points, respectively).

The responder analyses on HAQ-DI, FACIT-Fatigue and SF-36 (mentioned above under the first bullet point) used by the company are not considered for the dossier assessment. As explained in the *General Methods* of the Institute [1], for a response criterion to reflect with sufficient certainty a patient-noticeable change, predefined, it should correspond to at least 15% of the scale range of an instrument. This is not the case with the response criteria presented. Alternatively, post-hoc analyses can be presented with exactly 15% of the scale range. As the company provided these analyses for all symptom outcomes (see third bullet point above), they are used for the assessment.

However, contrary to the information provided by the company, the response criterion in the company’s post-hoc analyses on health-related quality of life, assessed with the SF-36, does not represent 15% of the scale range (for the assessment, see Appendix C of the full dossier assessment). These analyses are therefore not taken into account. In the present assessment, the continuous analyses are used for the benefit assessment for the SF-36 due to the lack of suitable responder analyses.

The responder analyses used by the company to assess the added benefit are presented in Appendix B of the full dossier assessment.

Follow-up observation

The company described in Module 4 A that all outcome were observed also beyond the end of therapy. This is appropriate. Despite this longer follow-up observation, in the analyses presented by the company in Module 4 A, recordings were only taken into account up to the discontinuation of the study medication. Values after discontinuation of the study medication as well as missing values in responder analyses for binary outcomes were imputed using non-responder imputation (NRI). For MMRM analyses of continuous outcomes, values after discontinuation of the study medication were set as missing. The company did not present analyses that included all observations recorded (i.e. also those after discontinuation of the study medication). The proportion of < 20% of the patients who ended therapy prematurely is taken into account in the risk of bias (see Section 2.4.2.2).

2.4.2.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: filgotinib + MTX vs. adalimumab + MTX

Study	Study level	Outcomes															
		All-cause mortality	Clinical remission (CDAI ≤ 2.8) ^a		Low disease activity (CDAI ≤ 10) ^b		Tender joints ^c	Swollen joints ^c	Pain (VAS)	Patient assessment of disease activity (VAS)	Physical functioning (HAQ-DI)	Fatigue (FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Infections (SOC, AE) ^d
FINCH 1	L	L	H ^e	H ^e	L	L	H ^e	H ^e	H ^e	H ^e	H ^e	H ^e	L	L	L	L	L

a. Supplementary presentation: SDAI ≤ 3.3 and Boolean definition, see Appendix B of the full dossier assessment.
 b. Supplementary presentation: SDAI ≤ 11 and DAS28 (CRP) ≤ 3.2, see Appendix B of the full dossier assessment.
 c. Based on 28 joints.
 d. All AEs of the MedDRA SOC “infections and infestations” are used for the recording of infections, and all SAEs for the recording of serious infections.
 e. High proportion of patients who were rated as non-responders due to missing values or discontinuation of the study medication.

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

Concurring with the company, the risk of bias was rated as low for the results of the categories of all-cause mortality, health-related quality of life, for all outcomes of the category of side effects, and for the morbidity outcomes of tender and swollen joints.

For the results of the morbidity outcomes, apart from the 2 outcomes on joints mentioned above, the risk of bias was rated as high, which deviates from the assessment of the company. The reason for this is a high proportion of patients who were rated as non-responders due to missing values or discontinuation of the study medication (> 10% in both study arms). In the case of statistically significant results, sensitivity analyses (Institute's calculations using alternative imputation strategies according to Higgins 2008 [9]) were carried out for the present assessment besides the primary analysis, in which patients with missing values or after discontinuation of the study medication were imputed as non-responders, in order to check the robustness of the estimated effects.

Certainty of conclusions

As described in Section 2.4.1.2, it is unclear how many patients in the FINCH 1 study were not treated in compliance with the approval. The company did not provide any corresponding information in Module 4 A. These uncertainties lead overall to a reduced certainty of conclusions. On the basis of the effects shown in the FINCH 1 study, at most hints, e.g. of an added benefit, can therefore be derived for all outcomes.

2.4.2.3 Results

Table 12 and Table 13 summarize the results on the comparison of filgotinib + MTX with adalimumab + MTX in patients with moderate to severe active rheumatoid arthritis for whom a first therapy with bDMARDs or tsDMARDs is indicated.

Results on common AEs, SAEs and discontinuation due to AEs are presented in Appendix A of the full dossier assessment. Results on further operationalizations of clinical remission or low disease activity ($SDAI \leq 3.3$, Boolean definition, $SDAI \leq 11$ and $DAS28 (CRP) \leq 3.2$), as well as the responder analyses on physical functioning (HAQ-DI), fatigue (FACIT-Fatigue) and SF-36 considered by the company in its benefit assessment, are presented as supplementary information in Appendix B of the full dossier assessment.

Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Table 12: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: filgotinib + MTX vs. adalimumab + MTX (multipage table)

Study Outcome category Outcome Imputation strategy	Filgotinib + MTX		Adalimumab + MTX		Filgotinib + MTX vs. adalimumab + MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
FINCH 1					
Mortality					
All-cause mortality	475	3 (0.6)	325	1 (0.3)	2.05 [0.21; 19.65]; 0.53
Morbidity					
Clinical remission (CDAI ≤ 2.8)	475	140 (29.5)	325	74 (22.8)	1.29 [1.02; 1.64]; 0.035 ^{a, b}
Sensitivity analyses:					
NRI with variance correction	475	140 (29.5)	325	74 (22.8)	1.29 [0.99; 1.69]; 0.060 ^{c, d}
ACA ^e	399	140 (35.1)	265	74 (27.9)	1.26 [0.99; 1.59]; 0.057 ^c
ICA-pc with variance correction ^f	475	– (33.9)	325	– (27.9)	1.22 [0.96; 1.54]; 0.107 ^{c, d}
Low disease activity (CDAI ≤ 10)	475	318 (66.9)	325	199 (61.2)	1.09 [0.98; 1.21]; 0.11 ^{a, b}
Pain (VAS) ^g	475	329 (69.3)	325	217 (66.8)	1.03 [0.94; 1.14]; 0.48 ^{a, b}
Patient assessment of disease activity (VAS) ^g	475	348 (73.3)	325	223 (68.6)	1.06 [0.97; 1.16]; 0.22 ^{a, b}
Physical functioning (HAQ-DI) ^h	475	305 (64.2)	325	183 (56.3)	1.12 [1.00; 1.25]; 0.054 ^{a, b}
Fatigue (FACIT-Fatigue) ⁱ	475	239 (50.3)	325	156 (48.0)	1.04 [0.90; 1.20]; 0.62 ^{a, b}
Health status (EQ-5D VAS) ^g	475	254 (53.5)	325	167 (51.4)	1.02 [0.89; 1.17]; 0.75 ^{a, b}
Side effects					
AEs (supplementary information)	475	352 (74.1)	325	239 (73.5)	–
SAEs	475	35 (7.4)	325	22 (6.8)	1.09 [0.65; 1.82]; 0.75
Discontinuation due to AEs	475	26 (5.5)	325	18 (5.5)	0.99 [0.55; 1.77]; 0.97
Infections (SOC, AEs)	475	206 (43.4)	325	129 (39.7)	1.09 [0.92; 1.29]; 0.30
Serious infections (SOC, AE)	475	13 (2.7)	325	10 (3.1)	0.89 [0.39; 2.00]; 0.78

Table 12: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: filgotinib + MTX vs. adalimumab + MTX (multipage table)

Study Outcome category Outcome Imputation strategy	Filgotinib + MTX		Adalimumab + MTX		Filgotinib + MTX vs. adalimumab + MTX RR [95% CI]; p-value
	N	Patients with event n (%)	N	Patients with event n (%)	
<p>a. Effect estimation based on a generalized linear model (GLM) with treatment group and stratification factors.</p> <p>b. Imputation strategy NRI: Patients with missing values or after discontinuation of study medication are rated as non-responders.</p> <p>c. Institute's calculation, asymptotic.</p> <p>d. Institute's calculation, estimation of variance according to the dataset re-sizing approach (approach W3 in [9]).</p> <p>e. Analysis is exclusively based on patients with complete observation.</p> <p>f. In both treatment groups, the missing values are imputed according to the observed risk in the control group.</p> <p>g. Patients with improvement of ≥ 15 mm or points (corresponds to 15% of the scale range).</p> <p>h. Patients with improvement of ≥ 0.45 points (corresponds to 15% of the scale range).</p> <p>i. Patients with improvement of ≥ 7.8 points (corresponds to 15% of the scale range).</p> <p>ACA: available case analysis; AE: adverse event; CDAI: Clinical Disease Activity Index; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; ICA-pc: imputed case analysis according to risk in the control group; MTX: methotrexate; n: number of patients with (at least one) event; N: number of analysed patients; NRI: non-responder imputation; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus</p>					

Table 13: Results (morbidity and health-related quality of life, continuous) – RCT, direct comparison: filgotinib + MTX vs. adalimumab + MTX

Study Outcome category Outcome	Filgotinib + MTX			Adalimumab + MTX			Filgotinib + MTX vs. adalimumab + MTX
	N ^a	Values at baseline mean (SD)	Change at week 52 mean (SD)	N ^a	Values at baseline mean (SD)	Change at week 52 mean (SD)	MD [95% CI]; p-value ^b
FINCH 1							
Morbidity							
Tender joints ^c	400	11 (5.2)	-10 (5.1)	265	11 (5.0)	-10 (4.7)	0 [-1; 0]; 0.013
Swollen joints ^c	400	15 (6.4)	-13 (6.0)	265	15 (6.3)	-12 (5.8)	-1 [-1; 0]; 0.014
Health-related quality of life							
SF-36^d							
Physical Component Summary	399	33.4 (7.17)	12.0 (8.73)	265	32.8 (7.74)	12.4 (9.21)	0.1 [-1.0; 1.3]; 0.81
Mental Component Summary	399	43.9 (10.44)	6.7 (10.53)	265	44.1 (10.44)	6.7 (9.90)	0.2 [-1.1; 1.5]; 0.79
Physical functioning	399	34.4 (22.77)	31.1 (26.54)	265	34.2 (23.80)	32.1 (25.59)	-0.3 [-3.7; 3.1]
Physical role functioning	399	39.0 (21.22)	28.9 (23.99)	265	38.5 (21.84)	27.6 (25.90)	2.3 [-0.9; 5.5]
Bodily pain	399	33.1 (16.45)	32.6 (22.64)	265	31.4 (16.30)	33.7 (24.60)	0.5 [-2.5; 3.6]
General health perception	399	39.2 (16.87)	19.0 (18.87)	265	38.0 (16.93)	19.5 (20.20)	0.1 [-2.5; 2.7]
Vitality	399	40.4 (18.45)	22.1 (20.56)	265	38.6 (17.56)	23.3 (21.88)	0.6 [-2.2; 3.3]
Social functioning	399	56.8 (24.45)	21.1 (26.33)	265	55.7 (24.03)	22.6 (26.17)	-0.6 [-3.7; 2.6]
Emotional role functioning	399	59.2 (26.50)	19.7 (26.97)	265	60.9 (25.50)	19.2 (23.84)	0.3 [-2.7; 3.3]
Mental wellbeing	399	56.3 (18.70)	15.1 (19.39)	265	56.4 (18.42)	14.4 (19.15)	0.7 [-1.8; 3.2]
<p>a. Number of patients with values at week 52; the values at baseline may be based on other patient numbers.</p> <p>b. Effect estimation based on MMRM analysis with baseline value, treatment group, and visits as categorical variables, stratification factors and treatment*visit interaction as fixed effect and patients as random effect.</p> <p>c. Based on 28 joints.</p> <p>d. Higher values indicate better health-related quality of life; a positive group difference indicates an advantage of filgotinib + MTX.</p> <p>CI: confidence interval; MD: mean difference; MMRM: mixed-effects model with repeated measures; MTX: methotrexate; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form 36 Health Survey; vs.: versus</p>							

On the basis of the available data, no more than hints, e.g. of an added benefit, can be determined for all outcomes (see Section 2.4.2.2).

Mortality

All-cause mortality

There was no statistically significant difference between the treatment groups for the outcome “all-cause mortality”. This resulted in no hint of an added benefit of filgotinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

This concurs with the company’s assessment.

Morbidity

Clinical remission (CDAI)

A statistically significant difference in favour of filgotinib + MTX was shown for the outcome “clinical remission” based on the $CDAI \leq 2.8$. The sensitivity analyses using alternative imputation strategies did not confirm this effect regarding statistical significance, however (see Table 12). This resulted in a hint of an added benefit of filgotinib + MTX in comparison with adalimumab + MTX.

This deviates from the assessment of the company, which overall derived an indication of an added benefit on the basis of the $CDAI \leq 2.8$, the $SDAI \leq 3.3$ and the Boolean definition.

Low disease activity (CDAI)

No statistically significant difference between the treatment groups was shown for the outcome “low disease activity” on the basis of the $CDAI \leq 10$. This resulted in no hint of an added benefit of filgotinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

This deviates from the assessment of the company, which overall derived an indication of an added benefit on the basis of the $CDAI \leq 10$, the $SDAI \leq 11$, and the $DAS28 (CRP) \leq 3.2$.

Tender joints

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

This deviates from the approach of the company, which presented the results for the outcome “tender joints” as supplementary information, but did not use this outcome for the derivation of the added benefit.

Swollen joints

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

This deviates from the approach of the company, which presented the results for the outcome “swollen joints” as supplementary information, but did not use this outcome for the derivation of the added benefit.

Pain (VAS)

For the outcome “pain” (VAS), no statistically significant difference between the treatment groups was shown based on the responder analysis with an improvement of ≥ 15 points. This resulted in no hint of an added benefit of filgotinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company, which also derived no hint of an added benefit for this outcome on the basis of continuous analyses.

Patient assessment of disease activity (VAS)

For the outcome “patient assessment of disease activity” (VAS), no statistically significant difference between the treatment groups was shown based on the responder analysis with an improvement of ≥ 15 points. This resulted in no hint of an added benefit of filgotinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven in each case.

This concurs with the assessment of the company, which also derived no hint of an added benefit for this outcome on the basis of continuous analyses.

Physical functioning (HAQ-DI)

For the outcome “physical functioning” (HAQ-DI), no statistically significant difference between the treatment groups was shown based on the responder analysis with an improvement of ≥ 0.45 points. This resulted in no hint of an added benefit of filgotinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

This concurs with the assessment of the company, which also derived no hint of an added benefit on the basis of a response criterion of 0.22 points.

Fatigue (FACIT-Fatigue)

For the outcome “fatigue” (FACIT-Fatigue), no statistically significant difference between the treatment groups was shown based on the responder analysis with an improvement of

≥ 7.8 points. This resulted in no hint of an added benefit of filgotinib + MTX in comparison with adalimumab + MTX; an added benefit is therefore not proven.

This concurs with the assessment of the company, which also derived no hint of an added benefit on the basis of a response criterion of 4 points.

Health status (EQ-5D VAS)

For the outcome “health status” (EQ-5D VAS), no statistically significant difference between the treatment groups was shown based on the responder analysis with an improvement of ≥ 15 points. This resulted in no hint of an added benefit of filgotinib + MTX in comparison with adalimumab + MTX for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company, which also derived no hint of an added benefit for this outcome on the basis of continuous analyses.

Health-related quality of life

SF-36 – Physical and Mental Component Summary

For the Physical and the Mental Component Summary of the SF-36, there was no statistically significant difference between the treatment groups on the basis of the continuous analyses. In each case, this resulted in no hint of an added benefit of filgotinib + MTX in comparison with adalimumab + MTX.

For both the Physical and for the Mental Component Summary of the SF-36, this corresponds to the assessment of the company, which, on the basis of responder analyses with an improvement of ≥ 5 points, also derived no hint of an added benefit.

Side effects

SAEs, discontinuation due to AEs

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

This concurs with the company’s assessment for both outcomes.

Infections, serious infections

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

This deviates from the approach of the company, which presented the results for the outcomes “infections” and “serious infections”, but did not use them for the derivation of the added benefit.

2.4.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered in the present assessment:

- age (< 65 years/≥ 65 years)
- sex (male/female)
- high disease activity at baseline (DAS28 [CRP] ≤ 5.1 [no high activity]/DAS28 [CRP] > 5.1 [high activity])

Apart from the outcomes “tender joints” and “swollen joints” and the continuous analyses of the SF-36, the company presented subgroup analyses for all outcomes relevant to the present benefit assessment.

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

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

There was no relevant effect modification with a statistically significant and relevant effect for any of the available subgroup analyses of the considered effect modifiers on patient-relevant outcomes at week 52.

2.4.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

2.4.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.4.2 (see Table 14).

Determination of the outcome category for symptom outcomes

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they are serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Clinical remission

The outcome “clinical remission” is assigned to the outcome category of serious/severe symptoms/late complications, as it can be assumed on the basis of the information on disease activity at baseline that the majority of the patients had serious/severe symptoms at this time point (see Table 8).

Table 14: Extent of added benefit at outcome level: filgotinib + MTX vs. adalimumab + MTX (multipage table)

Outcome category Outcome	Filgotinib + MTX vs. adalimumab + MTX Proportion of events (%) or mean change Effect estimation [95% CI]; p-value Probability^a	Derivation of extent^b
Mortality		
All-cause mortality	0.6% vs. 0.3% RR: 2.05 [0.21; 19.65]; p = 0.53	Lesser benefit/added benefit not proven
Morbidity		
Clinical remission CDAI ≤ 2.8	29.5% vs. 22.8% RR: 1.29 [1.02; 1.64]; p = 0.035 RR ^c 0.78 [0.61; 0.98] probability: “hint”	Outcome category: serious/severe symptoms/late complications 0.90 ≤ CI _u < 1.00 added benefit, extent: “minor”
Low disease activity CDAI ≤ 10	66.9% vs. 61.2% RR: 1.09 [0.98; 1.21]; p = 0.11	Lesser benefit/added benefit not proven
Tender joints ^d	Mean change: -10 vs. -10 MD: 0 [-1; 0]; p = 0.013 ^e	Lesser benefit/added benefit not proven
Swollen joints ^d	Mean change: -13 vs. -12 MD: -1 [-1; 0]; p = 0.014 ^e	Lesser benefit/added benefit not proven
Physical functioning (HAQ-DI) ^f	64.2% vs. 56.3% RR: 1.12 [1.00; 1.25]; p = 0.054	Lesser benefit/added benefit not proven
Fatigue (FACIT-Fatigue) ^g	50.3% vs. 48.0% RR: 1.04 [0.90; 1.20]; p = 0.62	Lesser benefit/added benefit not proven
Pain (VAS) ^h	69.3% vs. 66.8% RR: 1.03 [0.94; 1.14]; p = 0.48	Lesser benefit/added benefit not proven
Patient assessment of disease activity ^h	73.3% vs. 68.6% RR: 1.06 [0.97; 1.16]; p = 0.22	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS) ^h	53.5% vs. 51.4% RR: 1.02 [0.89; 1.17]; p = 0.75	Lesser benefit/added benefit not proven

Table 14: Extent of added benefit at outcome level: filgotinib + MTX vs. adalimumab + MTX (multipage table)

Outcome category Outcome	Filgotinib + MTX vs. adalimumab + MTX Proportion of events (%) or mean change Effect estimation [95% CI]; p-value Probability^a	Derivation of extent^b
Health-related quality of life		
SF-36		
Physical Component Summary	Mean change: 12.0 vs. 12.4 MD: 0.1 [-1.0; 1.3]; p = 0.81	Lesser benefit/added benefit not proven
Mental Component Summary	Mean change: 6.7 vs. 6.7 MD: 0.2 [-1.1; 1.5]; p = 0.79	Lesser benefit/added benefit not proven
Side effects		
SAEs	7.4% vs. 6.8% RR: 1.09 [0.65; 1.82]; p = 0.75	Greater/lesser harm not proven
Discontinuation due to AEs	5.5% vs. 5.5% RR: 0.99 [0.55; 1.77]; p = 0.97	Greater/lesser harm not proven
Infections (SOC, AEs)	43.4% vs. 39.7% RR: 1.09 [0.92; 1.29]; p = 0.30	Greater/lesser harm not proven
Serious infections (SOC, AE)	2.7% vs. 3.1% RR: 0.89 [0.39; 2.00]; p = 0.78	Greater/lesser harm not proven
<p>a. Probability provided if there is a statistically significant and relevant effect.</p> <p>b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).</p> <p>c. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.</p> <p>d. Based on 28 joints.</p> <p>e. Since the CI includes a difference of < 1 joint, it cannot be inferred that there is a relevant effect.</p> <p>f. Patients with improvement of ≥ 0.45 points (corresponds to 15% of the scale range).</p> <p>g. Patients with improvement of ≥ 7.8 points (corresponds to 15% of the scale range).</p> <p>h. Patients with improvement of ≥ 15 mm or points (corresponds to 15% of the scale range).</p> <p>AE: adverse event; CDAI: Clinical Disease Activity Index; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; MD: mean difference; MTX: methotrexate; RR: relative risk; SAE: serious adverse event; SF-36: Short Form 36 Health Survey; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus</p>		

2.4.3.2 Overall conclusion on added benefit

Table 15 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of filgotinib + MTX in comparison with adalimumab + MTX

Positive effects	Negative effects
Serious/severe symptoms/late complications ▪ Clinical remission (CDAI \leq 2.8): hint of an added benefit – extent: “minor”	-
Only data are available for the subpopulation of patients for whom a combination therapy with MTX is an option. No data are available for patients for whom monotherapy with filgotinib is an option.	
CDAI: Clinical Disease Activity Index; MTX: methotrexate	

Overall, there is exclusively one positive effect of filgotinib + MTX in comparison with adalimumab + MTX for adult patients for whom a first therapy with bDMARDs or tsDMARDs is indicated. This positive effect is not accompanied by negative effects.

In summary, there is a hint of a minor added benefit of filgotinib + MTX in comparison with the ACT for patients with moderate rheumatoid arthritis for whom a first therapy with bDMARDs or tsDMARDs is indicated and who have normal renal function or mild renal function disorder (CrCl \geq 60 mL/min).

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

Patients with renal function disorder

Only very few patients with moderate or severe renal function disorder were included in the FINCH 1 study. The company provided a descriptive presentation of the results for these patients from the study arms of filgotinib 100 mg + MTX (approved dose for these patients) versus adalimumab + MTX in the Appendix (see Section 2.4.1.2 for details). The qualitative consideration of the results led to justified doubts about the transferability of the results described above to the subpopulation of patients with moderate or severe renal function disorder (CrCl 15 to $<$ 60 mL/min). For example, the directions of effect for the outcomes on clinical remission, low disease activity and side effects consistently reverse. The added benefit of filgotinib + MTX in comparison with the ACT therefore only relates to the group of patients with normal renal function or mild renal function disorder (CrCl \geq 60 mL/min).

The assessment described above deviates from that of the company. The company derived an indication of a minor added benefit for filgotinib in combination with MTX for all patients for whom a first therapy with bDMARDs or tsDMARDs is indicated, irrespective of renal function.

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

2.5.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on filgotinib (status: 3 August 2020)
- bibliographical literature search on filgotinib (last search on 3 August 2020)
- search in trial registries/trial results databases for studies on filgotinib (last search on 5 August 2020)
- search on the G-BA website for filgotinib (last search on 5 August 2020)

To check the completeness of the study pool:

- search in trial registries for studies on filgotinib (last search on 20 October 2020)

The company presented no study for research question 3. No relevant study was identified from the check either.

2.5.2 Results on added benefit

The company presented no data for the assessment of the added benefit of filgotinib in comparison with the ACT for adult patients with inadequate response or intolerance to pretreatment with one or more bDMARDs and/or tsDMARDs. This resulted in no hint of an added benefit of filgotinib in comparison with the ACT. An added benefit is therefore not proven.

2.5.3 Probability and extent of added benefit

The company presented no data for the assessment of the added benefit of filgotinib in adult patients who have responded inadequately to, or who have not tolerated prior treatment with one or more bDMARDs and/or tsDMARDs. An added benefit of filgotinib in comparison with the ACT is therefore not proven for these patients.

This concurs with the assessment of the company, which claimed no added benefit for this patient group.

2.6 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of filgotinib + MTX in comparison with the ACT is summarized in Table 16.

Table 16: Filgotinib – probability and extent of added benefit

Subindication	ACT ^a	Probability and extent of added benefit
Adults with moderate to severe active rheumatoid arthritis		
Patients without poor prognostic factors ^b who have responded inadequately to, or who have not tolerated prior treatment with one disease-modifying antirheumatic drug (csDMARD ^c , including methotrexate [MTX])	Alternative csDMARDs ^c if suitable (e.g. MTX, leflunomide) as monotherapy or combination therapy	Added benefit not proven
Patients for whom a first therapy with bDMARDs or tsDMARDs is indicated ^d	bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability)	Combination with MTX: ▪ hint of minor added benefit ^e
		Monotherapy: added benefit not proven
Patients who have responded inadequately to, or who have not tolerated prior treatment with one or more bDMARDs and/or tsDMARDs	Switching of bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance or unsuitability; or, in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on prior therapy ^f	Added benefit not proven
<p>a. Presentation of the respective ACT specified by the G-BA.</p> <p>b. Poor prognostic factors: detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antigen antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.</p> <p>c. In the G-BA's specification of the ACT, csDMARDs are referred to as "classical DMARDs". The present benefit assessment uses the term "csDMARDs".</p> <p>d. This comprises both patients with poor prognostic factors who have responded inadequately to, or who have not tolerated prior treatment with one csDMARD (including MTX), and patients who have responded inadequately to or have not tolerated prior treatment with several csDMARDs (including MTX).</p> <p>e. The added benefit relates exclusively to patients with normal renal function or mild renal function disorder (CrCl \geq 60 mL/min).</p> <p>f. Switching the mode of action should be considered depending on the prior therapy.</p> <p>ACT: appropriate comparator therapy; bDMARD: biologic DMARD; CrCl: creatinine clearance; csDMARD: conventional synthetic DMARD; DAS: Disease Activity Score; DAS28: DAS based on 28 joints; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate; tsDMARD: targeted synthetic DMARD</p>		

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.
2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. *Biom J* 2016; 58(1): 43-58. <https://dx.doi.org/10.1002/bimj.201300274>.
3. Gilead Sciences. A randomized, double-blind, placebo- and active-controlled, multicenter, phase 3 study to assess the efficacy and safety of filgotinib administered for 52 weeks in combination with methotrexate to subjects with moderately to severely active rheumatoid arthritis who have an inadequate response to methotrexate [online]. [Accessed: 29.10.2020]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-000568-41.
4. Gilead Sciences. Filgotinib in combination with methotrexate in adults with moderately to severely active rheumatoid arthritis who have an inadequate response to methotrexate (FINCH 1) [online]. 2019 [Accessed: 29.10.2020]. URL: <https://ClinicalTrials.gov/show/NCT02889796>.
5. Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010; 69(9): 1580-1588. <https://dx.doi.org/10.1136/ard.2010.138461>.
6. Gilead. Jyseleca Filmtabletten [online]. 2020 [Accessed: 03.12.2020]. URL: <https://www.fachinfo.de>.
7. Amgen. AMGEVITA 20 mg/40 mg Injektionslösung in einer Fertigspritze; AMGEVITA 40 mg Injektionslösung im Fertigpen [online]. 2020 [Accessed: 03.12.2020]. URL: <https://www.fachinfo.de>.
8. Smolen JS, Landewe RBM, Bijlsma JWJ et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020; 79(6): 685-699. <https://dx.doi.org/10.1136/annrheumdis-2019-216655>.
9. Higgins JPT, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. *Clin Trials* 2008; 5(3): 225-239. <https://dx.doi.org/10.1177/1740774508091600>.

The full report (German version) is published under
<https://www.iqwig.de/en/projects/a20-90.html>.