IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A17-39

# Sarilumab (rheumatoid arthritis) –

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

## Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Sarilumab (Rheumatoide Arthritis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 November 2017). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

# Publishing details

**Publisher:**
Institute for Quality and Efficiency in Health Care

**Topic:**
Sarilumab (rheumatoid arthritis) – Benefit assessment according to §35a Social Code Book V

**Commissioning agency:**
Federal Joint Committee

**Commission awarded on:**
15 August 2017

**Internal Commission No.:**
A17-39

**Address of publisher:**
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**Keywords:** sarilumab, arthritis – rheumatoid, benefit assessment, NCT02332590

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**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| ACPA | anti-citrullinated protein antibody |
| ACR | American College of Rheumatology |
| ACT | appropriate comparator therapy |
| AE | adverse event |
| bDMARD | biologic disease-modifying antirheumatic drug |
| cDMARD | conventional disease-modifying antirheumatic drug |
| CDAI | Clinical Disease Activity Index |
| CI | confidence interval |
| DAS28-4 ESR | Disease-Activity-Score-28-4-erythrocyte sedimentation rate |
| DMARD | disease-modifying antirheumatic drug |
| EQ-5D | European Quality of Life-5 dimensions |
| EULAR | European League Against Rheumatism |
| FACIT-Fatigue | Functional Assessment of Chronic Illnes 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 |
| MCS | mental component summary |
| MTX | methotrexate |
| RA | rheumatoid arthritis |
| PCS | physical component summary |
| RAID | Rheumatoid Arthritis Impact of Disease-Score |
| RCT | randomized controlled trial |
| SAEs | serious adverse events |
| SDAI | Simplified Disease Activity Index |
| SF-36v2 | Short Form 36 – Version 2 Health Survey |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SMD | standardized mean difference |
| 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 sarilumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 15 August 2017.

### Research question

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

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

Table 2: Research questions of the benefit assessment of sarilumab in patients with moderate to severe active rheumatoid arthritis

| **Research question** | **Therapeutic indication** | **ACT[a]** |
|---|---|---|
| 1 | Patients without poor prognostic factors[b] who have not responded well enough to or have not tolerated previous treatment with 1 DMARD (conventional DMARD[c], including MTX) | Alternative conventional DMARDs, if suitable (e.g. MTX, leflunomide) as monotherapy or combination therapy |
| 2 | bDMARD-naive patients for whom a first treatment with biologic DMARDs (bDMARDs) is indicated[d] | bDMARD in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance |
| 3 | Patients who have not responded well enough to or have not tolerated previous treatment with 1 or several bDMARDs | Switching of bDMARD treatment (adalimumab or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab; in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in MTX intolerance; or in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on prior therapy.<br>Switching the mechanism of action should be considered depending on the prior therapy |

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Poor prognostic factors, such as detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.
c: In the report referred to as cDMARD.
d: This pertains both to patients with poor prognostic factors who have responded inadequately to or have not tolerated previous treatment with 1 DMARD (conventional DMARDs, including MTX) and to patients who have responded inadequately to or have not tolerated previous treatment with several disease-modifying antirheumatic drugs (conventional DMARDs, including MTX).
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; cDMARD: conventional disease-modifying antirheumatic drug; DAS: Disease Activity Score; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate

The company followed the ACT specified by the G-BA and, from the possible options, chose adalimumab for research question 2.

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

**Results**

The study MONARCH, which compared sarilumab with adalimumab (each as monotherapy), was included in the benefit assessment of sarilumab in comparison with the ACT. Due to its design and the patients included, the MONARCH study was suitable to derive conclusions on the added benefit of sarilumab for a part of research question 2 based on a subpopulation.

For research questions 1 and 3, no data were available for the benefit assessment of sarilumab in comparison with the ACT. An added benefit is therefore not proven.

**Research question 2**

***Study characteristics***

The MONARCH study was a randomized, multicentre, double-blind, parallel-group phase 3 study on the comparison of sarilumab with adalimumab (each as monotherapy). The study included adult patients who had active rheumatoid arthritis and high disease activity. The patients should not have received prior treatment with biologic DMARDs (bDMARDs) or a targeted synthetic DMARD (tsDMARD). However, prior therapies with one or several disease-modifying antirheumatic drugs (cDMARDs), e.g. MTX, were allowed. The patients were allocated in a 1:1 ratio to treatment with sarilumab or adalimumab. The allocation was stratified by region.

Treatment with sarilumab and adalimumab was administered as subcutaneous injection every 2 weeks, which is in compliance with the approval. The planned double-blind randomized treatment phase was 24 weeks, in the subsequent open-label treatment phase patients in the adalimumab arm could also receive treatment with sarilumab.

***Relevant subpopulation for research question 2***

In the MONARCH study, both sarilumab and adalimumab were used as monotherapy. The included patients had already been pretreated with at least 1 cCMARD before the start of the study. Among other participants, the MONARCH study included patients with high disease activity who – according to the physician's assessment – were either intolerant to MTX or unsuitable for continued treatment with MTX after this pretreatment. This patient group was the relevant subpopulation for research question 2 of the present benefit assessment, since it corresponded to the approval of sarilumab as monotherapy (in case of MTX intolerance). This subpopulation comprised 87 patients in the intervention arm and 82 patients in the comparator arm.

Moreover, the MONARCH study also included patients who had responded inadequately to previous treatment with MTX, but were not intolerant to MTX (97 patients in the intervention arm and 103 patients in the comparator arm). However, according to the approval this patient group was not to be treated with a sarilumab monotherapy, but with a combination of sarilumab and MTX, and was therefore not relevant for the present benefit assessment.

The MONARCH study therewith provided data only for a part of research question 2, namely for patients who were treated with a sarilumab monotherapy in compliance with the approval. Data for patients of research question 2 who would have had to be treated with a combination therapy with MTX are missing.

***Risk of bias***

The risk of bias at study level was rated as low. At outcome level, the risk of bias was rated as high for the outcomes of the category "morbidity" and "quality of life", and as low for the outcomes of the category "mortality" and "adverse events".

***Results for research question 2: bDMARD-naive patients for whom a first treatment with bDMARDs is indicated***

*Patients who are suitable for treatment with MTX*

Data for patients who are suitable for treatment with MTX (subpopulation of research question 2) are not available.

*Patients with MTX intolerance*

One relevant study was available for the assessment of sarilumab in patients with MTX intolerance (subpopulation of research question 2). Due to the low risk of bias, at most an indication of an added benefit can therefore be derived for the outcomes of the categories "mortality" and "adverse events". Due to the high risk of bias of all outcomes, at most a hint of an added benefit can be derived for the outcomes of the categories "morbidity" and "health-related quality of life".

*Mortality*

- All-cause mortality

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality". Hence, there was no hint of an added benefit of sarilumab in comparison with adalimumab for this outcome; an added benefit is therefore not proven.

*Morbidity*

- Remission (Clinical Disease Activity Index [CDAI] ≤ 2.8, Simplified Disease Activity Index [SDAI] ≤ 3.3, Boolean definition according to American College of Rheumatology [ACR]/ European League Against Rheumatism [EULAR])

The outcome "remission" is operationalized using the 3 remission criteria CDAI ≤ 2.8, SDAI ≤ 3.3 or the Boolean definition according to ACR/EULAR. Assessment of the remission was primarily based on the CDAI ≤ 2.8.

There was no statistically significant difference between the treatment groups for all 3 remission criteria. Hence, there was no hint of an added benefit of sarilumab in comparison with adalimumab for the outcome "remission"; an added benefit is therefore not proven.

- Low disease activity (Disease-Activity-Score-28-4-erythrocyte sedimentation rate) [DAS28-4 ESR] < 3.2; SDAI ≤ 11, CDAI ≤ 10)

The outcome "low disease activity" is operationalized using the 3 criteria DAS28-4 ESR < 3.2, SDAI ≤ 11 or CDAI ≤ 10. Assessment of the low disease activity is primarily based on the DAS28-4 ESR < 3.2. There was a statistically significant difference between the treatment groups in favour of sarilumab for all 3 criteria. This resulted in a hint of an added benefit of sarilumab in comparison with adalimumab for the outcome "low disease activity".

- Physical functioning (Health Assessment Questionnaire-Disability Index [HAQ-DI])

A statistically significant difference between the treatment groups in favour of sarilumab was shown for the number of responders for the outcome "physical functioning" (improvement in HAQ-DI by ≥ 0.22 points). This resulted in a hint of an added benefit of sarilumab in comparison with adalimumab for this outcome.

- Pain (visual analogue scale [VAS])
- Global assessment of the disease activity by the patients (VAS)

A statistically significant difference for the mean change in favour of sarilumab was shown for the outcomes "pain" (VAS) and "global assessment of the disease activity" by the patients. The standardized mean difference in the form of Hedges' g was considered in each case to check the relevance of the result. The 95% confidence interval (CI) of the standardized mean difference (SMD) was completely below the irrelevance threshold of -0.2. This was interpreted to be a relevant effect. This resulted in a hint of an added benefit of sarilumab in comparison with adalimumab for these outcomes.

- Health status (European Quality of Life-5 Dimensions [EQ-5D] VAS)
- Morning stiffness (VAS)

For the outcomes "health status" (EQ-5D VAS) and morning stiffness (VAS), a statistically significant difference in favour of sarilumab was shown for the mean change. The standardized mean difference in the form of Hedges' g was considered to check the relevance of the result. The 95% CI was not fully outside the irrelevance range [−0.2; 0.2]. It could therefore not be inferred that the effect was relevant. Hence, there was no hint of an added benefit of sarilumab in comparison with adalimumab for these outcomes; an added benefit is therefore not proven.

- Swollen joint count

For the outcome "swollen joint count", a statistically significant difference in favour of sarilumab was shown for the mean change. This average difference amounted to about 1 joint. This group difference was not relevant. This was supported by consideration of the standardized mean difference in the form of Hedges' g (the 95% CI was not fully outside the

irrelevance range [−0.2; 0.2]). Hence, there was no hint of an added benefit of sarilumab in comparison with adalimumab for this outcome; an added benefit is therefore not proven.

- Tender joint count
- Fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-Fatigue])

No statistically significant difference between the treatment groups was shown for the outcomes "tender joint count" and "fatigue" (FACIT-Fatigue: number of responders). Hence, there was no hint of an added benefit of sarilumab in comparison with adalimumab for these outcomes; an added benefit is therefore not proven.

*Health-related quality of life*

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

For the physical component summary of the SF-36v2 acute, a statistically significant difference in favour of sarilumab was shown for the mean change. The standardized mean difference (SMD) in the form of Hedges' g was considered to check the relevance of the result. The 95% CI of the SMD was fully above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect. This resulted in a hint of an added benefit of sarilumab in comparison with adalimumab for this outcome.

- SF-36 acute – mental component summary (MCS)

For the mental component summary of the SF-36v2 acute, no statistically significant difference between the treatment groups was shown for the mean change. Hence, there was no hint of an added benefit of sarilumab in comparison with adalimumab for this outcome; an added benefit is therefore not proven.

*Side effects*

- Serious adverse events (SAEs)
- Discontinuation due to adverse events (AEs)
- Infections
- Serious infections

No statistically significant difference between the treatment groups was shown for the outcomes "SAEs", "discontinuation due to AEs", "infections" and "serious infections". Hence, for these outcomes, there was no hint of greater or lesser harm from sarilumab in comparison with adilumab; greater or lesser harm is therefore not proven.

**Research question 2: probability and extent of added benefit, patient groups with therapeutically important added benefit[2]**

*Patients who are suitable for treatment with MTX*

Data for patients who are suitable for treatment with MTX (subpopulation of research question 2) are not available, an added benefit is not proven for this patient group.

*Patients with MTX intolerance*

In summary, only positive effects, which were to be allocated to the outcome categories "morbidity" and "health-related quality of life", were found for bDMARD-naive patients for whom a first treatment with a bDMARD was indicated and who were intolerant to MTX (subpopulation of research question 2).

In the category "morbidity", there was a hint of a major added benefit for the outcome "low disease activity" and a hint of a minor added benefit for the outcome "physical functioning". In addition, there was a hint of a non-quantifiable added benefit for the outcomes "pain" (VAS) and "global assessment of the disease activity" by the patients (VAS).

In the category "health-related quality of life" there was a hint of a non-quantifiable added benefit for the outcome "physical component summary" of the SF-36v2 acute questionnaire.

In summary, there is a hint of a major added benefit of sarilumab in comparison with adalimumab for the subpopulation of the bDMARD-naive patients for whom a first treatment with a bDMARD is indicated and who are intolerant to MTX.

The added benefit with the extent "major" only exists for patients for whom achievement of lower disease activity is the treatment goal because achievement of a remission has become impossible. The treatment goal for all other patients is the achievement of a remission to prevent further joint damage. The major added benefit at outcome level for the outcome "low disease activity" is therefore only of subordinate relevance for these patients. There is an added benefit based on further positive effects also for patients for whom remission is still a treatment goal. The extent must be assessed to be at least minor. However, it remained unclear for which proportions of the relevant study population remission was still a relevant treatment goal and what the results for the outcome "remission" for these patients looked like. The added benefit for these patients is therefore rated as non-quantifiable.

[2] 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 ess benefit). For further details see [1,2].

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

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

Table 3: Sarilumab – probability and extent of added benefit

| Research question | Therapeutic indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|---|
| 1 | Patients without poor prognostic factors[b] who have not responded well enough to or have not tolerated previous treatment with 1 DMARD (conventional DMARD[c], including MTX) | Alternative conventional DMARDs, if suitable (e.g. MTX, leflunomide) as monotherapy or combination therapy | Added benefit not proven |
| 2 | bDMARD-naive patients for whom a first treatment with bDMARDs is indicated[d] | bDMARD in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance | Patients who are suitable for treatment with MTX: added benefit not proven |
| | | | Patients with MTX intolerance<br>▪ Patients with potential treatment goal "remission": hint of a non-quantifiable added benefit<br>▪ Patients for whom remission is no longer a treatment goal: hint of a major added benefit |
| 3 | Patients who have not responded well enough to or have not tolerated previous treatment with 1 or several bDMARDs | Switching of bDMARD treatment (adalimumab or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab; in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in MTX intolerance; or in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on prior therapy<br>Depending on prior therapy, switching the mechanism of action should be considered | Added benefit not proven |

(continued)

Table 3: Sarilumab – probability and extent of added benefit (continued)

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Poor prognostic factors, such as detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.
c: In the report referred to as cDMARD.
d: This pertains to both patients with poor prognostic factors who have responded inadequately to or have not tolerated previous treatment with 1 DMARD and patients who have responded inadequately to or have not tolerated previous treatment with several disease-modifying antirheumatic drugs.
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; cDMARD: conventional disease-modifying antirheumatic drug; DAS: Disease Activity Score; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate

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

## 2.2 Research question

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

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

Table 4: Research questions of the benefit assessment of sarilumab in patients with moderate to severe active rheumatoid arthritis

| **Research question** | **Therapeutic indication** | **ACT[a]** |
|---|---|---|
| 1 | Patients without poor prognostic factors[b] who have not responded well enough to or have not tolerated previous treatment with 1 DMARD (conventional DMARD[c], including MTX) | Alternative conventional DMARDs, if suitable (e.g. MTX, leflunomide) as monotherapy or combination therapy |
| 2 | bDMARD-naive patients for whom a first treatment with bDMARDs is indicated[d] | bDMARD in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance |
| 3 | Patients who have no responded well enough to or have not tolerated previous treatment with 1 or several bDMARDs | Switching of bDMARD treatment (adalimumab or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab; in combination with MTX; if applicable as monotherapy under consideration of the respective approval status in MTX intolerance; or, in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on prior therapy<br>Switching the mechanism of action should be considered depending on the prior therapy |

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Poor prognostic factors, such as detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.
c: In the report referred to as cDMARD.
d: This pertains to both patients with poor prognostic factors who have responded inadequately to or have not tolerated previous treatment with 1 DMARD (cDMARDs, including MTX) and patients who have responded inadequately to or have not tolerated previous treatment with several DMARDs (cDMARDs, including MTX).
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; cDMARD: conventional disease-modifying antirheumatic drug; DAS: Disease Activity Score; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate

After receipt of the dossier, the G-BA adjusted the ACT for the benefit assessment of sarilumab in patients with moderate to severe active rheumatoid arthritis in the course of the assessment procedure. Due to the changes performed by the G-BA, only 3 of originally 4 different research questions were considered. This means that all patients for whom a first treatment with bDMARDs is indicated are now considered jointly in a group (research

question 2) [3]. A detailed description of the composed patient groups can be found in Table 4 (footnote d).

The company followed the ACT specified by the G-BA and chose adalimumab from the possible options. However, the company based its presentation of the patient groups in the dossier on the distribution of the patient population applicable at the time of the dossier submission. At the same time, the company presented data for the composed population of the current research question 2 with its dossier; the difference had therefore no consequence for the present assessment (see Sections 2.8.1 and 2.8.2.1 of the full dossier assessment).

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

## 2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on sarilumab (status: 26 June 2017)
- bibliographical literature search on sarilumab (last search on 30 June 2017)
- search in trial registries for studies on sarilumab (last search on 30 June 2017)

To check the completeness of the study pool:

- search in trial registries for studies on sarilumab (last search on 22 August 2017)

The check identified no additional relevant study.

### 2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: sarilumab vs. adalimumab (each as monotherapy) (subpopulation of research question 2)

| Study | Study category | | |
|---|---|---|---|
| | Study for approval of the drug to be assessed (yes/no) | Sponsored study[a] (yes/no) | Third-party study (yes/no) |
| MONARCH | Yes | Yes | No |
| a: Study for which the company was sponsor.<br>RCT: randomized controlled trial; vs.: versus | | | |

The study MONARCH was included in the benefit assessment of sarilumab in comparison with the ACT, this corresponded to the company's approach. The study compared sarilumab with adalimumab, each as monotherapy. Due to its design and the patients included, the MONARCH study was suitable to derive conclusions on the added benefit of sarilumab for research question 2 based on a subpopulation (restricted to patients with MTX intolerance) (see also Section 2.5).

For research questions 1 and 3, no data were available for the benefit assessment of sarilumab in comparison with the ACT. The assessment of the data situation concurs with that of the company.

Table 6 shows an overview of the data presented by the company on the different research questions of the benefit assessment.

Table 6: Sarilumab – overview of the data available for the benefit assessment of sarilumab

| **Research question** | **Population** | **Data presented** |
|---|---|---|
| 1 | Patients without poor prognostic factors[a] who have not responded well enough to or have not tolerated previous treatment with 1 DMARD (conventional DMARD[b], including MTX) | – |
| 2[c] | bDMARD-naive patients for whom a first treatment with bDMARDs is indicated[d] | Patients who are suitable for treatment with MTX:<br>Patients with MTX intolerance:<br>RCT (subpopulation of the MONARCH study) |
| 3[e] | Patients who have no responded well enough to or have not tolerated previous treatment with 1 or several bDMARDs | – |

a: Poor prognostic factors, such as detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antibodies), high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.
b: In the report referred to as cDMARD.
c: Corresponds to research questions 2 and 3 of the company.
d: This pertains both to patients with poor prognostic factors who have responded inadequately to or have not tolerated previous treatment with 1 DMARD (conventional DMARDs, including MTX) and to patients who have responded inadequately to or have not tolerated previous treatment with several disease-modifying antirheumatic drugs (conventional DMARDs, including MTX).
e: Corresponds to research question 4 of the company.
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; cDMARD: conventional disease-modifying antirheumatic drug; DAS: Disease Activity Score; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate

Section 2.5.4 contains a reference list for the study included for research question 2.

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

### 2.4.1 Results on added benefit (research question 1)

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

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

The company presented no data for the assessment of the added benefit of sarilumab in patients without poor prognostic factors who have responded inadequately or were intolerant to prior treatment with 1 cDMARD. An added benefit of sarilumab 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.

### 2.4.3 List of included studies (research question 1)

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

## 2.5 Research question 2: bDMARD-naive patients for whom a first treatment with bDMARDs is indicated

### 2.5.1 Study characteristics

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

Table 7: Characteristics of the included study – RCT, direct comparison: sarilumab vs. adalimumab (each as monotherapy) (subpopulation of research question 2)

| Study | Study design | Population | Interventions (numbers of randomized patients) | Study duration | Location and period of study | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|
| MONARCH | RCT, double-blind, parallel | Adult patients with active rheumatoid arthritis[b] who<br>▪ were either intolerant to MTX or unsuitable for continued treatment with MTX,<br>*or*<br>▪ showed inadequate response to treatment with MTX after at least 12 weeks | Total population[c]<br>Sarilumab (N = 184)<br>Adalimumab (N = 185)<br><br>Relevant subpopulation thereof[d]:<br>Sarilumab (n = 87)<br>Adalimumab (n = 82) | Screening:<br>4 weeks<br><br>Treatment:<br>24 weeks<br><br>Non-randomized extension phase[e]:<br>Max. 276 weeks<br><br>Follow-up:<br>6 weeks (in case of treatment discontinuation during randomized treatment phase) | 86 centres in 14 countries, divided into 3 regions:<br>region 1 (Western countries): Czech Republic, Germany, Hungary, Israel, Spain, USA<br>Region 2 (South America): Chile, Peru<br>Region 3 (other): Poland, Romania, Russia, South Africa, South Korea, Ukraine<br><br>02/2015–01/2016<br>(the extension phase will end about 2020) | primarily:<br>Change of the DAS28-ESR after 24 week<br>Secondary: morbidity, health-related quality of life, AEs |

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for this benefit assessment.
b: The patients were to have high disease activity (DAS28-4 ESR > 5.1).
c: This population was not relevant for the assessment and is not shown in the following tables. Besides the patient group relevant for the benefit assessment, it includes the patient group with inadequate response to MTX, for whom sarilumab monotherapy was not an option according to the approval, but who were to be treated with a sarilumab-MTX combination therapy.
d: Group of patients who were intolerant to MTX, including: patients who had been pretreated with a cDMARD (sarilumab [N = 35]; adalimumab [N = 35]) and patients who had been pretreated with ≥ 2 cDMARDs (sarilumab [N = 52]; adalimumab [N = 47]).
e: All patients who advanced from the double-blind to the open-label, non-randomized extension phase, received 200 mg sarilumab as subcutaneous injection at 2-week intervals.

AE: adverse event; cDMARD: conventional DMARD; DAS28-4 ESR: Disease-Activity-Score-28-4-erythrocyte sedimentation rate; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 8: Characteristics of the intervention – RCT, direct comparison: sarilumab vs. adalimumab (each as monotherapy) (subpopulation of research question 2)

| Study | Sarilumab | Adalimumab | Prior and concomitant medication |
|---|---|---|---|
| MONARCH | Subcutaneous administration of sarilumab<br>200 mg every 2 weeks for 24 weeks<br><br>and<br>adalimumab placebo<br><br>Dose reduction not allowed | Subcutaneous administration of adalimumab<br>40 mg every 2 weeks for 24 weeks<br><br>and<br>sarilumab placebo<br><br>Administration frequency could be increased (to weekly administration) from week 16. | Prohibited prior therapy:<br>▪ Treatment with a biologic (bDMARD) against rheumatoid arthritis (RA)<br>▪ Treatment with a Janus kinase (JAK) inhibitor (tsDMARD, e.g. tofacitinib)<br><br>Allowed prior therapy:<br>▪ Treatment with a non-biologic DMARD<br><br>Prohibited concomitant treatment:<br>▪ bDMARDS<br>▪ cDMARDS<br>▪ Corticosteroid injections<br><br>Allowed concomitant treatment:<br>▪ Oral corticosteroids[a]<br>▪ Anti-inflammatory drugs and COX-2 inhibitors<br>▪ Lipid-lowering drugs |

a: ≤ 10 mg prednisone or equivalent; allowed at a stable dose ≥ 4 weeks prior to randomization.
COX-2: cyclooxygenase-2; bDMARD: biologic DMARD; cDMARD: conventional DMARD; DMARD: disease-modifying antirheumatic drug; JAK: Janus kinase; RA: rheumatoid arthritis; RCT: randomized controlled trial; tsDMARD: targeted synthetic DMARD; vs.: versus

The MONARCH study was a randomized, multicentre, double-blind, parallel-group phase 3 study on the comparison of sarilumab with adalimumab (in monotherapy). The study included adult patients with active rheumatoid arthritis who should have high disease activity.

The patients should not have received prior treatment with biotechnological DMARDs (bDMARDs) or a tsDMARD. However, prior therapies with one or several cDMARDs, e.g. MTX, were allowed. The patients were allocated in a 1:1 ratio to treatment with sarilumab or adalimumab. The allocation was stratified by region.

Treatment with sarilumab and adalimumab was provided as subcutaneous injection and additional placebo injection every 2 weeks, which is in compliance with the approval. The planned double-blind randomized treatment phase was 24 weeks, in the subsequent open-label treatment phase patients in the adalimumab arm could also receive treatment with sarilumab.

Primary outcome of the MONARCH study was the change of the DAS28-4 ESR after 24 weeks in comparison with the baseline value. Patient-relevant outcomes on morbidity, health-related quality of life and AEs were additionally recorded.

***Relevant subpopulation for research question 2***

In the MONARCH study, both sarilumab and adalimumab were used as monotherapy. The included patients had already been pretreated with at least 1 cCMARD before the start of the study. Among other participants, the MONARCH study included patients with high disease activity who – according to the physician's assessment – were either intolerant to MTX or unsuitable for continued treatment with MTX after this pretreatment. This patient group was the relevant subpopulation for research question 2 of the present benefit assessment, since it corresponded to the approval of sarilumab as monotherapy (in case of MTX intolerance). This subpopulation comprised 87 patients in the intervention arm and 82 patients in the comparator arm.

Moreover, the MONARCH study also included patients who had responded inadequately to previous treatment with MTX, but who were not intolerant to MTX (97 patients in the intervention arm and 103 patients in the comparator arm). However, according to the approval this patient group was not to be treated with a sarilumab monotherapy, but with a combination of sarilumab and MTX, and is therefore not relevant for the present benefit assessment.

The MONARCH study therewith provided data only for a part of research question 2, namely for patients who were treated with a sarilumab monotherapy in accordance with the approval status. Data for patients of research question 2 who would have had to be treated with a combination therapy with MTX are missing.

**Patient characteristics**

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

Table 9: Characteristics of the study population – RCT, direct comparison: sarilumab vs. adalimumab (each as monotherapy) (subpopulation of research question 2)

| **Study**<br>**Characteristics**<br>**Category** | **Sarilumab** | **Adalimumab** |
|---|---|---|
| **MONARCH** | N[a] = 87 | N[a] = 82 |
| Age [years], mean (SD) | 53 (13) | 54 (12) |
| Sex [F/M], % | 87/13 | 87/13 |
| Region, n (%) | | |
| Region 1 (Western countries) | 40 (46.0) | 31 (37.8) |
| Region 2 (South America) | 17 (19.5) | 24 (29.3) |
| Region 3 (others) | 30 (34.5) | 27 (32.9) |
| Disease duration: time between first diagnosis and randomization [years], mean (SD) | 9.35 (9.19) | 7.63 (8.60) |
| Functional status [HAQ-DI], mean (SD) | 1.70 (0.58) | 1.71 (0.72) |
| Tender joint count[b], mean (SD) | 27.72 (12.58) | 27.78 (13.69) |
| Swollen joint count[c], mean (SD) | 19.07 (10.80) | 19.30 (11.00) |
| Rheumatoid factor status, n (%) | | |
| Positive | 58 (69.0) | 49 (62.0) |
| Negative | 26 (31.0) | 30 (38.0) |
| ACPA status, n (%) | | |
| Positive | 66 (78.6) | 60 (75.9) |
| Negative | 18 (21.4) | 19 (24.1) |
| DAS28-4 ESR, MW (SD) | 6.89 (0.64) | 6.85 (0.82) |
| Number of previous cDMARDS, n (%) | | |
| 1 | 35 (40.2) | 35 (42.7) |
| 2 | 24 (27.6) | 25 (30.5) |
| ≥ 3 | 28 (32.2) | 22 (26.8) |
| Duration of the prior MTX therapy<br>Months; MW [min; max] | 45.44 [0.2; 279.6] | 50.41 [0.2; 359.2] |
| Treatment discontinuation, n (%) | 12 (13.8%) | 13 (15.9%) |
| Study discontinuation[d], n (%) | ND | ND |

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Based on 68 joints.
c: Based on 66 joints.
d: Only the number of patients who had not undergone follow-up observation until week 24 was provided: sarilumab arm: n = 6 (6.9%) and adalimumab arm n = 7 (8.5%).

ACPA: anti-citrullinated protein antibody; cDMARD: conventional disease-modifying antirheumatic drug; DAS28: Disease-Activity-Score 28; ESR: erythrocyte sedimentation rate; 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; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patient characteristics between the arms of the MONARCH study were balanced. The mean age of the patients was about 54 years, and the majority were female.

A majority of patients was seropositive (positive rheumatoid factor serostatus and/or positive anti-citrullinated peptide antibodies [ACPA] serostatus). According to the inclusion criteria of the MONARCH study, all patients had high disease activity (Disease-Activity-Score-28-4-erythrocyte sedimentation rate [DAS28-4 ESR] > 5.1), which was determined between screening and randomization. At the time point of randomization, the mean DAS28-4 ESR was about 6.9 in both treatment groups.

The distribution of the disease characteristics shows that patients in both study arms were patients with poor prognostic factors.

About 41% of the patients had been treated with only 1 cDMARD prior to the start of the study, which, according to the inclusion criteria, was MTX. Besides MTX, the remaining 59% of the patients had already received other cDMARDS before the start of the study.

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

**Risk of bias at study level**

Table 10 shows the risk of bias at study level.

Table 10: Risk of bias at study level – RCT, direct comparison: sarilumab vs. adalimumab (each as monotherapy) (subpopulation of research question 2)

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

The risk of bias at study level for the MONARCH study was rated as low. This concurs with the company's assessment.

### 2.5.2 Results on added benefit (research question 2)

#### 2.5.2.1 Outcomes included (research question 2)

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.8.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - remission
  - low disease activity
  - tender joint count
  - swollen joint count
  - pain, measured using a visual analogue scale (VAS)
  - global assessment of the disease activity by the patients, measured using a VAS
  - health status, measured using the EQ-5D VAS
  - morning stiffness, measured using a VAS
  - fatigue, measured using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
  - physical functioning, measured using the HAQ-DI
- Health-related quality of life
  - measured with the physical and mental component summary of the SF-36v2 acute
- Side effects
  - serious adverse event (SAE)
  - discontinuation due to AEs
  - infections
  - serious Infections
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.8.2.4.3 of the full dossier assessment).

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

Table 11: Matrix of outcomes – RCT, direct comparison: sarilumab vs. adalimumab (each as monotherapy) (subpopulation of research question 2)

| Study | Outcomes | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **All-cause mortality** | **Remission (SDAI ≤ 3.3; CDAI ≤ 2.8; Boolean definition)** | **Low disease activity (DAS28-ESR < 3.2; SDAI ≤ 11; CDAI ≤ 10)** | **Tender joint count[a]** | **Swollen joint count[a]** | **Pain (VAS)** | **Global assessment of the disease activity by the patients (VAS)** | **Health status (EQ-5D VAS)** | **Morning stiffness (VAS)** | **Fatigue (FACIT-F)** | **Physical functioning[b] (HAQ-DI)** | **Health-related quality of life (SF-36v2 acute)** | **SAEs** | **Discontinuation due to AEs** | **Infections[c]** | **Serious infections[d]** |
| MONARCH | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |

a: Based on 28 joints.
b: Including activities of daily living.
c: AEs of the SOC "infections and infestations".
d: SAEs of the SOC "infections and infestations".

AE: adverse event; CDAI: Clinical Disease Activity Index; DAS: Disease Activity Score; EQ-5D: European Quality of Life-5 Dimensions; ESR: erythrocyte sedimentation rate; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SDAI: Simplified Disease Activity Index; SF-36v2: Short Form (36) – version 2 Health Survey; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus; Y: yes

#### 2.5.2.2 Risk of bias (research question 2)

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

Table 12: Risk of bias at study and outcome level – RCT, direct comparison: sarilumab vs. adalimumab (each as monotherapy) (subpopulation of research question 2)

| Study | Study level | Outcomes | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | All-cause mortality | Remission (SDAI ≤ 3.3; CDAI ≤ 2.8; Boolean definition) | Low disease activity (DAS28-ESR < 3.2; SDAI ≤ 11; CDAI ≤ 10) | Tender joint count[a] | Swollen joint count[a] | Pain (VAS) | Global assessment of the disease activity by the patients (VAS) | Health status (EQ-5D VAS) | Morning stiffness (VAS) | Fatigue (FACIT-F) | Physical functioning[b] (HAQ-DI) | Health-related quality of life (SF-36v2 acute) | SAEs | Discontinuation due to AEs | Infections[c] | Serious infections[d] |
| MONARCH | L | L | H[e] | H[e] | H[f] | H[f] | H[f] | H[f] | H[f] | H[f] | H[e] | H[e] | H[f] | L | L | L | L |

a: Based on 28 joints.
b: Including activities of daily living.
c: AEs of the SOC "infections and infestations".
d: SAEs of the SOC "infections and infestations".
e: The proportion of imputed values in the responder analysis is unknown, see Section 2.8.2.4.2 of the full dossier assessment.
f: Number of patients included in the analysis unclear, see Section 2.8.2.4.2 of the full dossier assessment.

AE: adverse event; CDAI: Clinical Disease Activity Index; DAS: Disease Activity Score; EQ-5D: European Quality of Life-5 Dimensions; ESR: erythrocyte sedimentation rate; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; H: high; L: low; PtGA: Patient's Global Assessment; RAID: Rheumatoid Arthritis Impact of Disease-Score; RCT: randomized controlled trial; SAE: serious adverse event; SDAI: Simplified Disease Activity Index; SF-36v2: Short Form (36) – version 2 Health Survey; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The risk of bias was rated as high for the outcomes of the categories “morbidity” and “quality of life”. This was due to the fact that the information on the number of patients for whom values were imputed was missing for the responder analyses. Due to the number of patients who discontinued their treatment, this information was missing for at least 15% of the participants. This problem likewise applies to the analyses of continuous data of these outcome categories. The risk of bias for all other outcomes was rated as low.

These estimations of the risk of bias at outcome level deviate from those of the company, which rated the risk of bias as low for all outcomes used.

A detailed description for the assessment of the risk of bias can be found in Section 2.8.2.4.2 of the full dossier assessment.

#### 2.5.2.3 Results (research question 2)

Table 13 and Table 14 summarize the results on the comparison of sarilumab with adalimumab in bDMARD-naive patients with MTX intolerance and active rheumatoid arthritis for whom a first treatment with bDMARDs is indicated. Where necessary, the data from the company’s dossier were supplemented with the Institute’s calculations. Results on common AEs are presented in Table 23 and Table 24 of Appendix A of the full dossier assessment.

Table 13: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: sarilumab vs. adalimumab (each as monotherapy) (subpopulation of research question 2)

| Study<br>Outcome category<br>Outcome<br>Time point | Sarilumab | | Adalimumab | | Sarilumab vs. adalimumab |
|---|---|---|---|---|---|
| | N[a] | Patients with event n (%) | N[a] | Patients with event n (%) | RR [95% CI]; p-value[b] |
| **MONARCH (week 24)** | | | | | |
| **Mortality** | | | | | |
| All-cause mortality (week 24) | 87 | 1 (1.1) | 82 | 0 | 2.83 [0.12; 68.49]; 0.515[c] |
| **Morbidity** | | | | | |
| Remission[d] | | | | | |
| CDAI ≤ 2.8 | 87 | 8 (9.2) | 82 | 2 (2.4) | 3.37 [0.73; 15.45]; 0.118 |
| SDAI ≤ 3.3 | 87 | 9 (10.3) | 82 | 2 (2.4) | 3.75 [0.83; 16.88]; 0.084 |
| Boolean definition[e] | 87 | 5 (5.7) | 82 | 2 (2.4) | 2.20 [0.43; 11.16]; 0.342 |
| Low disease activity[f] | | | | | |
| DAS28-ESR < 3.2 | 87 | 39 (44.8) | 82 | 8 (9.8) | 4.22 [2.10; 8.46]; < 0.001 |
| SDAI ≤ 11 | 87 | 40 (46.0) | 82 | 16 (19.5) | 2.29 [1.40; 3.74]; 0.001 |
| CDAI ≤ 10 | 87 | 39 (44.8) | 82 | 15 (18.3) | 2.39 [1.44; 3.97]; < 0.001 |
| Physical functioning (HAQ-DI)[g] | 87 | 58 (66.7) | 82 | 40 (48.8) | 1.37 [1.05; 1.78]; 0.021 |
| Fatigue (FACIT-Fatigue)[h] | 87 | 58 (66.7) | 82 | 43 (52.4) | 1.27 [0.99; 1.64]; 0.063 |
| **Side effects** | | | | | |
| AEs (supplementary information) | 87 | 58 (66.7) | 82 | 56 (68.3) | – |
| SAEs | 87 | 4 (4.6) | 82 | 5 (6.1) | 0.75 [0.21; 2.72]; 0.666 |
| Discontinuation due to AEs | 87 | 7 (8.0) | 82 | 3 (3.7) | 2.20 [0.59; 8.26]; 0.242 |
| Infections[i] | 87 | 25 (28.7) | 82 | 23 (28.0) | 1.02 [0.63; 1.66]; 0.921 |
| Serious Infections[j] | 87 | 2 (2.3%) | 82 | 0 (0) | 4.72 [0.23; 96.78]; 0.223[c] |

(continued)

Table 13: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: sarilumab vs. adalimumab (each as monotherapy) (subpopulation of research question 2) (continued)

a: In analyses for outcomes of the category "morbidity" missing values were imputed as non-responses. The proportion of imputed values is unknown.
b: unless stated otherwise, RR, 95% CI and p-value from generalized linear model.
c: Institute's calculation of RR, 95% CI (asymptotic) and p-value (unconditional exact test; CSZ method accordin to [4]); due to 0 events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms.
d: Assessment of the remission was primarily based on the CDAI ≤ 2.8.
e: Number of tender and swollen joints each ≤ 1, CRP ≤ 1 mg/dL, assessment of disease activity by the patient ≤ 1.
f: Assessment of the low disease activity was primarily based on the DAS28-4 ESR < 3.2.
g: Patients with improvement by ≥ 0.22 points.
h: Patients with improvement by ≥ 4 points.
i: AEs with PTs cited in the SOC "infections and infestations" in MedDRA V18.1.
j: SAEs with PTs cited in the SOC "infections and infestations" in MedDRA V18.1.

AE: adverse event; CDAI: Clinical Disease Activity Index; CI: confidence interval; CRP: C-reactive protein; DAS28: Disease-Activity-Score 28; ESR: erythrocyte sedimentation rate; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; MeDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SDAI: Simplified Disease Activity Index; SOC: System Organ Class: vs.: versus

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: sarilumab vs. adalimumab (each as monotherapy) (subpopulation of research question 2)

| Study<br>Outcome category | Sarilumab | | | Adalimumab | | | Sarilumab vs. adalimumab |
|---|---|---|---|---|---|---|---|
| Outcome | N[a] | Values at start of study mean (SD) | Change at week 24 mean[b] (SD) | N[a] | Values at start of study mean (SD) | Change at week 24 mean[b] (SD) | LSMD: [95% CI]; p-value |
| **MONARCH (24 weeks)** | | | | | | | |
| **Morbidity** | | | | | | | |
| Tender joint count[c] | 76 | 16.78 (5.54) | −11.93 (6.08) | 70 | 16.09 (6.50) | −9.78 (7.11) | −1.45 [−3.13; 0.22]; 0.089 |
| Swollen joint count[c] | 76 | 13.36 (5.35) | −10.70 (4.95) | 70 | 13.29 (5.53) | −9.06 (6.28) | −1.33 [−2.34; −0.33]; 0.010[d] |
| Morning stiffness (VAS)[e] | 76 | 73.16 (19.48) | −40.08 (29.74) | 70 | 67.43 (23.68) | −24.46 (27.37) | −10.97 [−18.84; −3.09]; 0.007<br>Hedges' g<br>−0.46 [−0.78; −0.13] |

(continued)

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: sarilumab vs. adalimumab (each as monotherapy) (subpopulation of research question 2) (continued)

| Study<br>Outcome category<br>Outcome | Sarilumab | | | Adalimumab | | | Sarilumab vs. adalimumab |
|---|---|---|---|---|---|---|---|
| | N[a] | Values at start of study mean (SD) | Change at week 24 mean[b] (SD) | N[a] | Values at start of study mean (SD) | Change at week 24 mean[b] (SD) | LSMD: [95% CI]; p-value |
| **MONARCH (24 weeks)** | | | | | | | |
| **Morbidity** | | | | | | | |
| Pain (VAS)[e] | 76 | 71.82 (19.85) | −38.75 (27.39) | 69 | 71.16 (20.86) | −27.30 (24.06) | −11.44 [−18.46; −4.42]; 0.002<br>Hedges' g: −0.52 [−0.85; −0.202] |
| Global assessment of the disease activity by the patients (VAS)[e] | 76 | 69.20 (17.75) | −37.38 (25.18) | 70 | 68.86 (19.81) | −23.81 (25.51) | −12.68 [−19.49; −5.87]; < 0.001<br>Hedges' g: −0.60 [−0.92; −0.28] |
| Health status (EQ-5D VAS)[f] | 76 | 42.96 (21.54) | 25.24 (26.39) | 68 | 40.37 (20.91) | 17.81 (26.20) | 9.24 [2.68; 15.81]; 0.006<br>Hedges' g: 0.46 [0.13; 0.79] |
| **Health-related quality of life** | | | | | | | |
| SF-36v2 acute | | | | | | | |
| Physical component summary[f] | 72 | 29.92 (5.61) | 9.07 (7.44) | 70 | 30.53 (6.09) | 5.43 (6.68) | 3.64 [1.40; 5.88]; 0.002<br>Hedges' g: 0.53 [0.204; 0.86] |
| Mental component summary[f] | 72 | 37.40 (11.97) | 9.71 (11.40) | 70 | 34.71 (11.95) | 8.61 (12.64) | 2.44 [−0.81; 5.68]; 0.140 |

a: Number of patients for whom one value was available at the start of the study and at week 24. The number of patients considered in the analysis for the calculation of the effect possibly deviated; see Section 2.8.2.4.2 of the full dossier assessment.
b: LSMD, 95% CI and p-value from mixed-effects model with repeated measures.
c: Based on 28 joints.
d: Hedges' g: −0.43 [−0.76; −0.11].
e: Low values (negative change) indicate improvement.
f: Higher values (positive change) indicate improvement.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; LSMD: least squares mean distance; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SF-36v2: Short Form 36 –version 2 Health Survey; VAS: visual analogue scale; vs.: versus

One relevant study was available for the assessment of sarilumab. Due to the low risk of bias, at most an indication of an added benefit can therefore be derived for the outcomes of the categories "mortality" and "adverse events". Due to the high risk of bias, at most a hint of an

added benefit can therefore be derived for the outcomes of the categories "morbidity" and "health-related quality of life" (see Section 2.5.2, and Section 2.8.2.4.2 of the full benefit assessment).

**Mortality**

***All-cause mortality***

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality". Hence, there was no hint of an added benefit of sarilumab in comparison with adalimumab for this outcome; an added benefit is therefore not proven.

This concurs with the company' assessment, which, however, deviating from the Institute, allocated the outcome "all-cause mortality" to the category "safety/tolerability" under the designation "AEs with fatal outcome".

**Morbidity**

***Remission***

The outcome "remission" is operationalized using the 3 remission criteria CDAI ≤ 2.8, SDAI ≤ 3.3 or the Boolean definition according to ACR/EULAR. Assessment of the remission was primarily based on the CDAI ≤ 2.8.

There was no statistically significant difference between the treatment groups for all 3 remission criteria. Hence, there was no hint of an added benefit of sarilumab in comparison with adalimumab for this outcome; an added benefit is therefore not proven.

This deviates from the company' assessment, which, in addition to the 3 criteria described above, included the remission criterion DAS28-4 ESR < 2.6 in its assessment, and derived an added benefit of sarilumab in comparison with adalimumab based on a statistically significant difference between the treatment groups.

***Low disease activity***

The outcome "low disease activity" is operationalized using the 3 criteria DAS28-4 ESR < 3.2, SDAI ≤ 11 or CDAI ≤ 10. The assessment of the low disease activity is primarily based on the DAS28-4 ESR < 3.2.

For all 3 criteria, there was a statistically significant difference between the treatment groups in favour of sarilumab. This resulted in a hint of an added benefit of sarilumab in comparison with adalimumab for this outcome.

This concurs with the company's assessment, however, the company derives an indication of an added benefit for this outcome due to the risk of bias assessed as low by the company.

***Tender joint count***

For the outcome "tender joint count", no statistically significant difference between the treatment groups was shown for the mean change. Hence, there was no hint of an added benefit of sarilumab in comparison with adalimumab for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment, which also derived no added benefit for the outcome "tender joints".

***Swollen joint count***

For the outcome "swollen joint count", a statistically significant difference in favour of sarilumab was shown for the mean change. This average difference amounted to about 1 joint. This group difference was not relevant. This was supported by consideration of the standardized mean difference in the form of Hedges' g (the 95% CI was not fully outside the irrelevance range [−0.2; 0.2]). Hence, there was no hint of an added benefit of sarilumab in comparison with adalimumab for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company, which also derived no added benefit for the outcome "swollen joints".

***Pain (VAS)***

For the outcome "pain" (VAS), a statistically significant difference in favour of sarilumab was shown for the mean change. The standardized mean difference in the form of Hedges' g was considered to check the relevance of the result. The 95% CI of the standardized SMD was completely below the irrelevance threshold of −0.2. This was interpreted to be a relevant effect. This resulted in a hint of an added benefit of sarilumab in comparison with adalimumab for this outcome.

This does not concur with the company's assessment, which for the outcome "pain" (VAS) considered a responder analysis with the response criterion "improvement by ≥ 20.4" as operationalization, and did not derive a corresponding added benefit.

***Global assessment of the disease activity by the patients (VAS)***

A statistically significant difference for the mean change in favour of sarilumab was shown for the outcome "global assessment of the disease activity by the patients". The standardized mean difference in the form of Hedges' g was considered to check the relevance of the result. The 95% CI of the SMD was fully below the irrelevance threshold of −0.2. This was interpreted to be a relevant effect. This resulted in a hint of an added benefit of sarilumab in comparison with adalimumab for this outcome.

This does not concur with the company's assessment, which for the outcome "disease activity" (VAS), considered a responder analysis with the response criterion "improvement by ≥ 18.4" as operationalization, and did not derive a corresponding added benefit.

***Health status (EQ-5D VAS)***

For the outcome "health status" (EQ-5D VAS), a statistically significant difference in favour of sarilumab was shown for the mean change. The standardized mean difference in the form of Hedges' g was considered to check the relevance of the result. The 95% CI was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect is relevant. Hence, there was no hint of an added benefit of sarilumab in comparison with adalimumab for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

***Morning stiffness (VAS)***

For the outcome "morning stiffness" (VAS), a statistically significant difference in favour of sarilumab was shown for the mean change. The standardized mean difference in the form of Hedges' g was considered to check the relevance of the result. The 95% CI was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect is relevant.

Hence, there was no hint of an added benefit of sarilumab in comparison with adalimumab for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

***Fatigue (FACIT-Fatigue)***

No statistically significant difference between the treatment groups was shown for the number of responders for the outcome "Fatigue" (improvement of the FACIT-Fatigue $\geq 4$). Hence, there was no hint of an added benefit of sarilumab in comparison with adalimumab for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

***Physical functioning (HAQ-DI)***

A statistically significant difference between the treatment groups in favour of sarilumab was shown for the number of responders for the outcome "physical functioning" (improvement in HAQ-DI by $\geq 0.22$ points). This resulted in a hint of an added benefit of sarilumab in comparison with adalimumab for this outcome.

This concurs with the company's assessment, which, however, used one supplementary response criterion (improvement in HAQ-DI by $\geq 0.375$ points) for the derivation of the added benefit. Moreover, the company derived an indication of an added benefit for this outcome due to the risk of bias that it assessed to be low.

**Health-related quality of life**

***SF-36 acute – physical component summary***

For the physical component summary of the SF-36v2 acute, a statistically significant difference in favour of sarilumab was shown for the mean change. The standardized mean difference in the form of Hedges' g was considered to check the relevance of the result. The 95% CI of the SMD was fully above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect.

This resulted in a hint of an added benefit of sarilumab in comparison with adalimumab for this outcome.

This does not concur with the company's assessment, which considered 3 different response criteria as operationalization for this outcome (improvement by ≥ 2.5, 5.1 and 7.2) and did not derive a corresponding added benefit for any of them. However, besides the SF-36 acute, it also used a responder analysis of the Rheumatoid Arthritis Impact of Disease-Score (RAID) instrument for the assessment of the health-related quality of life, and derived an added benefit of sarilumab on this basis.

***SF-36 acute – mental component summary***

For the mental component summary of the SF-36v2 acute, no statistically significant difference between the treatment groups was shown for the mean change.

Hence, there was no hint of an added benefit of sarilumab in comparison with adalimumab for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company, which derived no added benefit for the mental component summary of the SF-36v2.

**Side effects**

***SAEs, discontinuation due to AEs, infections and serious infections***

No statistically significant difference between the treatment groups was shown for the outcomes "SAEs", "discontinuation due to AEs", "infections" and "serious infections".

Hence, for these outcomes, there was no hint of greater or lesser harm from sarilumab in comparison with adilumab; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

### 2.5.2.4 Subgroups and other effect modifiers (research question 2)

The following subgroup characteristics were considered relevant for the present benefit assessment (see also Section 2.8.2.4.3 of the full dossier assessment):

- sex (men/women)

- age (< 65 years/≥ 65 years)
- Region (region 1 [Western countries] / region 2 [South America] / region 3 [other])
- number of previous cDMARDS (1/≥ 2)

The company presented (except for the characteristic "number of previous cDMARDS") no subgroup analyses for the analyses on the changes that had occurred since the start of the study for any of the outcomes.

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

There was no effect modification with a statistically significant interaction between treatment and subgroup characteristic for any of the remaining outcomes.

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

The derivation of probability and extent of added benefit for research question 2 at outcome level is shown below. The different outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on 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.

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

Research question 2 pertains to bDMARD-naive patients with active rheumatoid arthritis for whom a first treatment with a bDMARD is indicated. Sarilumab may either be used in combination with MTX or as monotherapy (in case of MTX intolerance or when treatment with MTX is unsuitable).

Only data on the sarilumab monotherapy in patients with MTX intolerance were available for the assessment.

For this patient group, the data presented in Section 2.5.2 resulted in the following assessments of sarilumab in comparison with adalimumab:

- one hint of an added benefit for each of the morbidity outcomes "low disease activity", "physical functioning" (HAQ-DI), "pain" (VAS) and "global assessment by the patients" (VAS),
- one hint of an added benefit for the physical component summary of the SF-36v2 acute.

**Determination of the outcome category for the outcomes "low disease activity", "physical functioning" (HAQ-DI), "pain" (VAS) and "global assessment of the disease activity by the patients" (VAS)**

The outcomes "low disease activity" and "physical functioning" (HAQ-DI) are allocated to the outcome category serious/severe symptoms/late complications, since supporting data are already available for this allocation [5,6]. This concurs with the company's assessment, which, however, justifies the allocation with the fact that the patients of the MONARCH study formed a patient group with severe rheumatoid arthritis, and all included morbidity outcomes were assessed as serious symptoms of the disease for this reason alone.

The outcomes "pain" (VAS) and "global assessment of the disease activity by the patients" (VAS) were allocated to the outcome category "non-serious/non-severe symptoms/late complications". The company provided no data that would justify the allocation of the values achieved for "pain" (VAS) and "global assessment of the disease activity by the patients" (VAS) in the relevant subpopulation of the MONARCH study to the outcome category "serious/severe symptoms/late complications". This assessment deviates from that of the company (see above).

The extent of the respective added benefit at outcome level was estimated from these results (see Table 15).

Table 15: Extent of added benefit at outcome level: sarilumab vs. adalimumab (each as monotherapy) (subpopulation of research question 2)

| **Outcome category**<br>**Outcome** | **Sarilumab vs. adalimumab**<br>**Proportion of patients with event or change**<br>**Effect [95% CI]; p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Mortality** | | |
| All-cause mortality | 1.1% vs. 0%<br>RR: 2.83 [0.12; 68.49]; p = 0.515 | Lesser benefit/added benefit not proven |
| **Morbidity** | | |
| Remission[c] | | |
| CDAI ≤ 2.8 | 9.2% vs. 2.4%<br>RR: 3.37 [0.73; 15.45]; p = 0.118 | Lesser benefit/added benefit not proven |
| SDAI ≤ 3.3 | 10.3% vs. 2.4%<br>RR: 3.75 [0.83; 16.88]; p = 0.084 | |
| Boolean definition | 5.7% vs. 2.4%<br>RR: 2.20 [0.43; 11.16]; p = 0.342 | |
| Low disease activity[d] | | |
| DAS28-ESR < 3.2 | 44.8% vs. 9.8%<br>RR: 4.22 [2.10; 8.46] p < 0.001<br>RR: 0.24 [0.12; 0.48][d]<br>Probability: "hint" | Outcome category: "serious/severe symptoms/late complications"<br>$CI_u$ < 0.75, risk ≥ 5%<br>added benefit, extent: "major" |
| SDAI ≤ 11 | 46.0% vs. 19.5%<br>RR: 2.29 [1.40; 3.74]; p = 0.001<br>RR: 0.44 [0.27; 0.71]e<br>Probability: "hint" | |
| CDAI ≤ 10 | 44.8% vs. 18.3%<br>RR: 2.39 [1.44; 3.97] p < 0.001<br>RR: 0.42 [0.25; 0.69][d]<br>Probability: "hint" | |
| Tender joint count[f] | −11.93 vs. −9.78<br>LSMD: −1.45 [−3.13; 0.22]<br>p = 0.089 | Lesser benefit/added benefit not proven |
| Swollen joint count[f] | −10.70 vs. −9.06<br>LSMD: −1.33 [−2.34; −0.33];<br>p < 0.010 | Lesser benefit/added benefit not proven |
| Morning stiffness (VAS)[h] | −40.08 vs. −24.46<br>LSMD: −10.97 [−18.84; −3.09]<br>p = 0.007<br>Hedges' g: −0,46 [−0.78; −0.13][i] | Lesser benefit/added benefit not proven |

(continued)

Table 15: Extent of added benefit at outcome level: sarilumab vs. adalimumab (each as monotherapy) (subpopulation of research question 2) (continued)

| **Outcome category**<br>**Outcome** | **Sarilumab vs. adalimumab**<br>**Proportion of patients with event or change**<br>**Effect [95% CI]; p-value**<br>**Probability[a]** | **Derivation of extent[b]** |
|---|---|---|
| **Morbidity** | | |
| Pain (VAS)[h] | −38.75 vs. −27.30<br>LSMD: −11.44 [−18.46; −4.42]<br>p = 0.002<br>Hedges' g: −0.52 [−0.85; −0.202][i]<br>probability: "hint" | Outcome category: "non-serious/non-severe symptoms/late complications"<br>added benefit, extent: "non-quantifiable" |
| Outcome category<br>Outcome | Sarilumab vs. adalimumab<br>Proportion of patients with event or change<br>Effect [95% CI]; p-value<br>Probability[a] | Derivation of extent[b] |
| Global assessment of the disease activity by the patients (VAS)[h] | −37.38 vs. −23.81<br>LSMD: −12.68 [−19.49; −5.87]<br>p < 0.001<br>Hedges' g: −0.60 [−0.92; −0.28][i]<br>Probability: "hint" | Outcome category: "non-serious/non-severe symptoms/late complications"<br>added benefit, extent: "non-quantifiable" |
| Health status (EQ-5D VAS) | 25.24 vs. 17.81<br>LSMD: 9.24 [2.68; 15.81] p = 0.006<br>Hedges' g: 0,46 [0.13; 0.79][i] | Lesser benefit/added benefit not proven |
| Fatigue (FACIT-Fatigue)[k] | 66.7% vs. 52.4%<br>RR: 1.27 [0.99; 1.64]; p = 0.063 | Lesser benefit/added benefit not proven |
| Physical functioning (HAQ-DI)[l] | 66.7% vs. 48.8%<br>RR: 1.37 [1.05; 1.78]; p = 0.021<br>RR: 0.73 [0.56; 0.95]e<br>Probability: "hint" | Outcome category: "serious/severe symptoms/late complications"<br>$0.90 \leq CI_u < 1.00$<br>added benefit, extent: "minor" |
| **Health-related quality of life** | | |
| SF-36v2 acute: physical sum score[j] | 9.07 vs. 5.43<br>LSMD: 3.64 [1.40; 5.88] p = 0.002<br>Hedges' g: 0.53 [0.204; 0.86][i]<br>Probability: "hint" | Outcome category: "health-related quality of life"<br>added benefit, extent: "non-quantifiable" |
| SF-36v2 acute: mental component summary[j] | 9.71 vs. 8.61<br>LSMD: 2.44 [-0.81; 5.68] p = 0.140 | Lesser benefit/added benefit not proven |

(continued)

Table 15: Extent of added benefit at outcome level: sarilumab vs. adalimumab (each as monotherapy) (subpopulation of research question 2) (continued)

| **Outcome category**<br>**Outcome** | **Sarilumab vs. adalimumab**<br>**Proportion of patients with event or change**<br>**Effect [95% CI]; p-value**<br>**Probability[a]** | **Derivation of extent[b]** |
|---|---|---|
| **Side effects** | | |
| SAEs | 4.6% vs. 6.1%<br>RR: 0.75 [0.21; 2.72]; p = 0.666 | Greater/lesser harm not proven |
| Discontinuation due to AEs | 8.0% vs. 3.7%<br>RR: 2.20 [0.59; 8.26]; p = 0.242 | Greater/lesser harm not proven |
| Infections | 28.7% vs. 28.0%<br>RR: 1.02 [0.63; 1.66]; p = 0.921 | Greater/lesser harm not proven |
| Serious infections | 2.3% vs. 0%<br>RR: 4.72 [0.23; 96.78]; p = 0.223 | Greater/lesser harm not proven |

a: Probability provided if a statistically significant and relevant effect was present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the $CI_u$.
c: Assessment of the remission was primarily based on the CDAI ≤ 2.8.
d: Assessment of the low disease activity was primarily based on the DAS28-4 ESR ≤ 3.2.
e: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
f: Based on 28 joints.
g: The mean difference amounted to about 1 joint. This group difference was not relevant.
h: Low values (negative change) indicate improvement.
i: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, it cannot be derived that a relevant effect is present.
j: Higher values (positive change) indicate improvement.
k: Patients with improvement by ≥ 4 points.
l: Patients with improvement by ≥ 0.22 points.

AE: adverse event; CDAI: Clinical Disease Activity Index; CI: confidence interval; DAS28: Disease Activity Score 28; EQ-5D: European Quality of Life-5 Dimensions; ESR: erythrocyte sedimentation rate; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; LSMD: Least-Squares-Mean Distance; RR: relative risk; SAE: serious adverse event; SDAI: Simplified Disease Activity Index; SF-36v2: Short Form (36) – version 2 Health Survey; VAS: visual analogue scale; vs.: versus;

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

Table 16 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of sarilumab in comparison with adalimumab (each as monotherapy) (research question 2)

| **Positive effects** | **Negative effects** |
|---|---|
| Serious/severe symptoms/late complications:<br>▪ Low disease activity: hint of an added benefit - extent: "major"<br>▪ Physical functioning (HAQ-DI): hint of an added benefit<br>– extent: "minor"<br>Non-serious/non-severe symptoms/late complications:<br>▪ Pain (VAS): hint of an added benefit – extent: "non-quantifiable"<br>▪ Global assessment of the disease activity by the patients (VAS): hint of an added benefit – extent: "non-quantifiable"<br>Health-related quality of life<br>▪ SF-36v2 acute, physical sum score: hint of an added benefit, extent: "non-quantifiable" | – |
| Only data on the subpopulation of patients with MTX intolerance were available for research question 2; data for patients who are suitable for treatment with MTX were missing. | |
| HAQ-DI: Health Assessment Questionnaire-Disability Index; SF-36v2: Short Form 36 – Version 2 Health Survey; VAS: visual analogue scale | |

In summary, only positive effects, which were to be allocated to the outcome categories "morbidity" and "health-related quality of life", were found for bDMARD-naive patients for whom a first treatment with a bDMARD was indicated and who were intolerant to MTX (subpopulation of research question 2).

In summary, there is a hint of a major added benefit of sarilumab in comparison with adalimumab for the subpopulation of the bDMARD-naive patients for whom a first treatment with a bDMARD is indicated and who are intolerant to MTX.

Moreover, the added benefit with the extent "major" only exists for patients for whom achievement of lower disease activity is the treatment goal because achievement of a remission is impossible. The treatment goal for all other patients is the achievement of a remission to prevent further joint damage. The major added benefit at outcome level for the outcome "low disease activity" is therefore only of subordinate relevance for these patients. There is an added benefit based on further positive effects also for patients for whom remission is still a treatment goal. The extent must be assessed to be at least minor. However, it remained unclear for which proportions of the relevant study population remission was still a relevant treatment goal and what the results for the outcome "remission" for these patients looked like. The added benefit for these patients is therefore rated as non-quantifiable.

Data for patients who are suitable for treatment with MTX (subpopulation of research question 2) are not available. An added benefit is not proven for this patient group.

The result of the assessment of the added benefit of sarilumab in comparison with the ACT is summarized in Table 17.

Table 17: Sarilumab – probability and extent of added benefit (research question 2)

| **Therapeutic indication** | **ACT**[a] | **Probability and extent of added benefit** |
|---|---|---|
| bDMARD-naive patients for whom a first treatment with bDMARDs is indicated[b] | bDMARD in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance | Patients who are suitable for treatment with MTX: added benefit not proven |
| | | Patients with MTX intolerance<br>▪ Patients with potential treatment goal "remission": hint of a non-quantifiable added benefit<br>▪ Patients for whom remission is no longer a treatment goal: hint of a major added benefit |
| a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.<br>b: This pertains to both patients with poor prognostic factors who have responded inadequately to or have not tolerated previous treatment with 1 DMARD (conventional DMARDs, including MTX) and to patients who have responded inadequately to or have not tolerated previous treatment with several DMARDs (conventional DMARDs, including MTX).<br>ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate | | |

The assessment described above deviates from that of the company, which derived an indication of a major added benefit for patients who were MTX-intolerant. The company also considered the added benefit for patients who are suitable for treatment with MTX as "not proven".

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

### 2.5.4 List of included studies (research question 2)

**MONARCH**

Burmester GR, Lin Y, Patel R, Van Adelsberg J, Mangan EK, Graham NMH et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. Ann Rheum Dis 2017; 76(5): 840-847.

Sanofi. Efficacy and safety of sarilumab and adalimumab monotherapy in patients with rheumatoid arthritis (SARIL-RA-MONARCH): full text view [online]. In: ClinicalTrials.gov. 15 September 2017 [accessed: 20 October 2017]. URL: https://ClinicalTrials.gov/show/NCT02332590.

Sanofi. Efficacy and safety of sarilumab and adalimumab monotherapy in patients with rheumatoid arthritis (SARIL-RA-MONARCH): study results [online]. In: ClinicalTrials.gov. 15 September 2017 [accessed: 19 October 2017]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02332590.

Sanofi. A randomized, double-blind, parallel-group study assessing the efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy in patients with rheumatoid arthritis; study EFC14092; clinical study report [unpublished]. 2016.

Sanofi Aventis Recherche & Development. A randomized, double-blind, parallel-group study assessing the efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy in patients with rheumatoid [online]. In: Clinical Trials Peruvian Registry. [Accessed: 30 August 2017]. URL: http://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=081-14.

Sanofi Aventis Recherche & Development. A randomized, double-blind, parallel-group study assessing the efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy in patients with rheumatoid arthritis [online]. In: EU Clinical Trials Register. [Accessed: 30 August 2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-002541-22.

## 2.6 Research question 3: patients with inadequate response or intolerance to pretreatment with 1 or several bDMARDs

### 2.6.1 Results on added benefit (research question 3)

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

### 2.6.2 Probability and extent of added benefit (research question 3)

The company presented no data for the assessment of the added benefit of sarilumab in patients with inadequate response or intolerance to prior treatment with 1 or several bDMARDs. An added benefit of sarilumab 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.

### 2.6.3 List of included studies (research question 3)

Not applicable as the company presented no data for research question 3 that are relevant for the benefit assessment.

## 2.7 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of sarilumab in comparison with the ACT is summarized in Table 18.

Table 18: Sarilumab – probability and extent of added benefit

| Research question | Therapeutic indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|---|
| 1 | Patients without poor prognostic factors[b] who have not responded well enough to or have not tolerated previous treatment with DMARD (conventional DMARD[c], including MTX) | Alternative conventional DMARDs, if suitable (e.g. MTX, leflunomide) as monotherapy or combination therapy | Added benefit not proven |
| 2 | bDMARD-naive patients for whom a first treatment with bDMARDs is indicated[d] | bDMARD in combination with MTX (**adalimumab** or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab), if applicable as monotherapy under consideration of the respective approval status in case of MTX intolerance | Patients who are suitable for treatment with MTX: added benefit not proven |
| | | | Patients with MTX intolerance<br>▪ Patients with potential treatment goal "remission": hint of a non-quantifiable added benefit<br>▪ Patients for whom remission is no longer a treatment goal: hint of a major added benefit |
| 3 | Patients who have not responded well enough to or have not tolerated previous treatment with 1 or several bDMARDs | Switching of bDMARD treatment (adalimumab or etanercept or certolizumab pegol or golimumab or abatacept or tocilizumab; in combination with MTX, if applicable as monotherapy under consideration of the respective approval status in MTX intolerance; or, in patients with severe rheumatoid arthritis, rituximab under consideration of the approval) depending on prior therapy.<br>Depending on prior therapy, switching the mechanism of action should be considered. | Added benefit not proven |

(continued)

Table 18: Sarilumab – probability and extent of added benefit (continued)

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: poor prognostic factors, such as detection of autoantibodies (e.g. rheumatoid factors, high level of anti-citrullinated peptide antibodies, high disease activity (determined with the DAS or the DAS28 assessment system, swollen joints, acute-phase reactants, e.g. C-reactive protein, erythrocyte sedimentation rate), early joint erosions.
c: In the report referred to as cDMARD.
d: This pertains to both patients with poor prognostic factors who have responded inadequately to or have not tolerated previous treatment with 1 DMARD and to patients who have responded inadequately to or have not tolerated previous treatment with several disease-modifying antirheumatic drugs.
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; cDMARD: conventional disease-modifying antirheumatic drug; DAS: Disease Activity Score; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; MTX: methotrexate

**Research questions 1 and 3**

No data for the assessment of the added benefit were available for patients with moderate to severe active rheumatoid arthritis without poor prognostic factors who have responded inadequately to or have not tolerated previous treatment with 1 cDMARD (research question 1) and for patients who have responded inadequately to or not tolerated previous treatment with 1 or several bDMARDs (research question 3). An added benefit of sarilumab versus the ACT is therefore not proven for these patients. This concurs with the company's assessment, which, however, noted that it considered research question 1 to be irrelevant for the benefit assessment of sarilumab.

**Research question 2**

For the derivation of the added benefit, bDMARD-naive patients with moderate to severe active rheumatoid arthritis for whom a first treatment with bDMARDs was indicated, were subdivided into patients who were candidates for a combination therapy with MTX and those who had to be treated with a sarilumab monotherapy due to MTX intolerance.

Data for the assessment of the added benefit for patients who are candidates for treatment with sarilumab in combination with MTX were not available. An added benefit of sarilumab versus the ACT is therefore not proven for these patients. This concurs with the company's assessment.

There is a hint of a major added benefit of sarilumab versus the ACT for those patients with MTX intolerance for whom remission is no longer a treatment goal. There is a hint of a non-quantifiable added benefit for patients with MTX intolerance for whom remission is no longer a treatment goal. This deviates from the approach of the company, which derived an indication of a major added benefit for all patients with MTX intolerance.

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

**References for English extract**

Please see full dossier assessment for full reference list.

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

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*The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a17-39-sarilumab-rheumatoid-arthritis-benefit-assessment-according-to-35a-social-code-book-v.7963.html.*