IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A18-14

Ixekizumab (psoriatic 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 *Ixekizumab (Psoriasis Arthritis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 May 2018). 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:
Ixekizumab (psoriatic arthritis) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
20 February 2018

Internal Commission No.:
A18-14

Address of publisher:
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Keywords: ixekizumab, arthritis – psoriatic, benefit assessment, NCT01695239

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[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
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD	biologic disease-modifying antirheumatic drug
BSA	body surface area
CASPAR	Classification for Psoriatic Arthritis
CI	confidence interval
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying antirheumatic drug
DLQI	Dermatology Life Quality Index
DMARD	disease-modifying antirheumatic drug
EQ-5D	European Quality of Life-5 Dimensions
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)
LDI-B	Leeds Dactylitis Index-Basic
LEI	Leeds Enthesitis Index
MCS	Mental Component Summary
MDA	minimal disease activity
NAPSI	Nail Psoriasis Severity Index
NRS	numeric rating scale
PAP	Patient Assessment of Pain
PASI	Psoriasis Area and Severity Index
PatGA	Patient Global Assessment of Disease Activity
PCS	Physical Component Summary
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
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 ixekizumab. 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 20 February 2018.

Research question

The aim of the present report was to assess the added benefit of ixekizumab in comparison with the appropriate comparator therapy (ACT) in the treatment of active psoriatic arthritis in patients who have responded inadequately to, or who have not tolerated one or more disease-modifying antirheumatic drugs (DMARDs).

For the benefit assessment of ixekizumab, the research questions presented in Table 2 resulted from the ACTs specified by the G-BA.

Table 2: Research questions of the benefit assessment of ixekizumab

Research question	**Subindication**	**ACT[a]**
1	Patients with active psoriatic arthritis without poor prognostic factors[b] who have responded inadequately to, or who have not tolerated prior treatment with a disease-modifying antirheumatic drug (conventional DMARDs, including methotrexate)	Alternative conventional DMARDs if suitable (methotrexate or leflunomide as monotherapy or combination therapy)
2	bDMARD-naive patients with active psoriatic arthritis for whom a first treatment with bDMARDs is indicated	TNF alpha inhibitor (**adalimumab** or etanercept or golimumab or infliximab), if applicable in combination with methotrexate
3	Patients with active psoriatic arthritis who have responded inadequately to, or who have not tolerated prior treatment with bDMARDs	Switch to a different bDMARD (adalimumab or etanercept or golimumab or infliximab), if applicable in combination with methotrexate

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: ≥ 5 affected joints; radiographic joint damage; increased inflammatory markers; extraarticular manifestations, particularly dactylitis.
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

In the course of the assessment of the dossier, the G-BA adapted the research questions and the ACTs for the benefit assessment of ixekizumab in patients with active psoriatic arthritis. Concurring with the consultation with the G-BA, the company based its dossier on the following 2 research questions: a) patients who have responded inadequately to prior treatment

with a DMARD, and b) patients who have responded inadequately to prior treatment with a biologic DMARD (bDMARD). Whereas research question b) is identical to research question 3 in Table 2, research questions 1 and 2 are subquestions of the original research question a). The dossier submitted by the company describes the added benefit of ixekizumab in patients with active psoriatic arthritis who have responded inadequately to prior treatment with a DMARD; the company assumed these patients to be patients who are candidates for treatment with a bDMARD for the first time (research question 2). These documents have remained relevant also after the G-BA changed patient groups and ACT.

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

Results for research questions 1 and 3

No data for the assessment of the added benefit of ixekizumab in comparison with the ACT were available for patients with active psoriatic arthritis without poor prognostic factors who have responded inadequately to, or who have not tolerated prior treatment with a DMARD (conventional DMARDs, including methotrexate) (research question 1) and for patients with active psoriatic arthritis who have responded inadequately to, or who have not tolerated prior treatment with bDMARDs (research question 3). An added benefit is therefore not proven.

Results for research question 2

Study RHAP was included in the benefit assessment for patients with active psoriatic arthritis who are candidates for treatment with a bDMARD for the first time (research question 2).

Study design

The RHAP study was a randomized, double-blind, active-controlled parallel group study. The relevant study arms compared ixekizumab with adalimumab. The study included patients with active psoriatic arthritis who have not been pretreated with a bDMARD.

A total of 208 patients were randomized to the relevant study arms and allocated to treatment with ixekizumab (N = 107) or adalimumab (N = 101).

The patients were treated in compliance with the recommendations of the respective Summaries of Product Characteristics (SPC). Treatment duration in both studies was 24 weeks. Follow-up observation was at least 12 weeks, irrespective of a participation in the extension phase.

Primary outcome of the study was the 20% improvement in American College of Rheumatology (ACR) criteria (ACR20). Secondary outcomes were disease activity, symptoms, health status, health-related quality of life, and side effects.

Subpopulation relevant for research question 2

According to the SPC of ixekizumab, the patients had to have responded inadequately to, or have not tolerated prior treatment with a DMARD. However, the RHAP study also included patients without prior DMARD treatment. In addition, the 4-week dosing interval administered in the relevant ixekizumab arm of the RHAP study is only approved for patients without concomitant moderate to severe plaque psoriasis. Patients with moderate to severe plaque psoriasis were also included in the study.

The company presented analyses of a subpopulation that, on the one hand, comprised only patients with DMARD pretreatment and, on the other, excluded patients with moderate to severe plaque psoriasis. The patients included in the subpopulation presented by the company (N = 51 in the ixekizumab arm and N = 56 in the adalimumab arm) were treated in compliance with the SPC of ixekizumab and were the basis for the present benefit assessment. However, only conclusions for patients without concomitant moderate to severe plaque psoriasis can be derived on the basis of this subpopulation.

Risk of bias

The risk of bias at study level was rated as low.

The risk of bias was rated as low for all outcomes, except for the following: minimal disease activity $(MDA)_{PASI}$, physical functioning (Health Assessment Questionnaire-Disability Index [HAQ-DI]), skin symptoms (Psoriasis Area and Severity Index [PASI] 100), and health-related quality of life (Dermatology Life Quality Index [DLQI]). For the mentioned outcomes, the risk of bias was rated as high. Based on the available data, at most hints, e.g. of an added benefit, can be determined for these outcomes because of the high risk of bias, and indications for all other outcomes.

Mortality

All-cause mortality

No death occurred in the relevant subpopulation during the study period. This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Morbidity

Minimal disease activity (MDA_{PASI}) and physical functioning (HAQ-DI)

There was no statistically significant difference between the treatment groups for the outcomes "minimal disease activity (MDA_{PASI})" and "physical functioning (HAQ-DI)". In each case, this resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Enthesitis (Leeds Enthesitis Index [LEI])

For the outcome "enthesitis (LEI)", a statistically significant difference in favour of ixekizumab was shown regarding the change from baseline in the number of tender entheses. The 95% confidence interval (CI) of the effect was [0.21; 1.15] entheses. The relevance of this result cannot be estimated with certainty. For this reason, the certainty of the result was downgraded for this outcome. This resulted in a hint of an added benefit of ixekizumab in comparison with adalimumab for the outcome "enthesitis".

Dactylitis (Leeds Dactylitis Index-Basic [LDI-B])

There was no statistically significant difference between the treatment groups for the outcome "dactylitis (LDI-B)". This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Nail psoriasis (Nail Psoriasis Severity Index [NAPSI])

There were no usable data for the outcome "nail psoriasis (NAPSI)". This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Skin symptoms (PASI 100)

A statistically significant difference in favour of ixekizumab was shown for the outcome "skin symptoms (PASI 100)". Due to the high risk of bias of the outcome, there was a hint of an added benefit of ixekizumab.

Health status (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS]), joint pain (Patient Assessment of Pain [PAP] VAS), patient-reported global disease activity (Patient Global Assessment of Disease Activity [PatGA] VAS), fatigue (Fatigue Severity numeric rating scale [NRS])

No statistically significant differences between the treatment groups were shown for any of the following outcomes: health status (EQ-5D VAS), joint pain (PAP VAS), patient-reported global disease activity (PatGA VAS), fatigue (Fatigue Severity NRS). In each case, this resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Disease activity of ankylosing spondylitis (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI])

No statistically significant difference between the treatment groups was shown for the outcome "disease activity of ankylosing spondylitis (BASDAI)". This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Tender joint count

For the outcome "tender joint count", a statistically significant difference in favour of ixekizumab was shown for the change from baseline. The 95% CI of the effect was [0.26; 6.07] joints. The relevance of this result cannot be estimated with certainty. For this reason, the certainty of the result was downgraded for this outcome. This resulted in a hint of an added benefit of ixekizumab in comparison with adalimumab for the outcome "tender joint count".

Swollen joint count

For the outcome "swollen joint count", a statistically significant difference in favour of ixekizumab was shown for the change from baseline. The 95% CI of the effect was [0.30; 2.99] joints. The relevance of this result cannot be estimated with certainty. For this reason, the certainty of the result was downgraded for this outcome. This resulted in a hint of an added benefit of ixekizumab in comparison with adalimumab for the outcome "swollen joint count".

Health-related quality of life

Short Form (36) Health Survey (SF-36)

For the SF-36, a statistically significant difference between the treatment groups was shown neither for the Physical Component Summary (PCS) nor for the Mental Component Summary (MCS). This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

DLQI

There was no statistically significant difference between the treatment groups for the outcome "DLQI". This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Side effects

Serious adverse events and discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". In each case, this resulted in no hint of lesser or greater harm of ixekizumab in comparison with adalimumab; greater or lesser harm is therefore not proven.

General disorders and administration site conditions

A statistically significant difference to the disadvantage of ixekizumab was shown for the specific AE "general disorders and administration site conditions". This resulted in an indication of greater harm from ixekizumab.

Infections and infestations

No statistically significant difference between the treatment groups was shown for the outcome "infections and infestations". This resulted in no hint of lesser or greater harm of ixekizumab in comparison with adalimumab; greater or lesser harm is therefore not proven.

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

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

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

Table 3: Ixekizumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Patients with active psoriatic arthritis without poor prognostic factors[b] who have responded inadequately to, or who have not tolerated prior treatment with a disease-modifying antirheumatic drug (conventional DMARDs, including methotrexate)	Alternative conventional DMARDs if suitable (methotrexate or leflunomide as monotherapy or combination therapy)	Added benefit not proven
2	bDMARD-naive patients with active psoriatic arthritis for whom a first treatment with bDMARDs is indicated	TNF alpha inhibitor (**adalimumab** or etanercept or golimumab or infliximab), if applicable in combination with methotrexate	Hint of minor added benefit[c]
3	Patients with active psoriatic arthritis who have responded inadequately to, or who have not tolerated prior treatment with bDMARDs	Switch to a different bDMARD (adalimumab or etanercept or golimumab or infliximab), if applicable in combination with methotrexate	Added benefit not proven

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: ≥ 5 affected joints; radiographic joint damage; increased inflammatory markers; extraarticular manifestations, particularly dactylitis.
c: Based on the data, a conclusion is only possible for patients without moderate to severe plaque psoriasis.
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

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

[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].

2.2 Research question

The aim of the present report was to assess the added benefit of ixekizumab in comparison with the ACT in the treatment of active psoriatic arthritis in patients who have responded inadequately to, or who have not tolerated one or more DMARDs.

For the benefit assessment of ixekizumab, the research questions presented in Table 4 resulted from the ACTs specified by the G-BA.

Table 4: Research questions of the benefit assessment of ixekizumab

Research question	**Subindication**	**ACT**[a]
1	Patients with active psoriatic arthritis without poor prognostic factors[b] who have responded inadequately to, or who have not tolerated prior treatment with a disease-modifying antirheumatic drug (conventional DMARDs, including methotrexate)	Alternative conventional DMARDs if suitable (methotrexate or leflunomide as monotherapy or combination therapy)
2	bDMARD-naive patients with active psoriatic arthritis for whom a first treatment with bDMARDs is indicated	TNF alpha inhibitor (**adalimumab** or etanercept or golimumab or infliximab), if applicable in combination with methotrexate
3	Patients with active psoriatic arthritis who have responded inadequately to, or who have not tolerated prior treatment with bDMARDs	Switch to a different bDMARD (adalimumab or etanercept or golimumab or infliximab), if applicable in combination with methotrexate

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: ≥ 5 affected joints; radiographic joint damage; increased inflammatory markers; extraarticular manifestations, particularly dactylitis.
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

In the present benefit assessment, the following terms are used for the research questions:

- Research question 1: patients with active psoriatic arthritis without poor prognostic factors
- Research question 2: patients with active psoriatic arthritis who are candidates for treatment with a bDMARD for the first time
- Research question 3: patients with active psoriatic arthritis who have responded inadequately to prior treatment with bDMARDs

In the course of the assessment of the dossier, the G-BA adapted the research questions and the ACTs for the benefit assessment of ixekizumab in patients with active psoriatic arthritis [3]. Concurring with the consultation with the G-BA, the company based its dossier on the following 2 research questions: a) patients who have responded inadequately to prior treatment with a DMARD, and b) patients who have responded inadequately to prior treatment with a bDMARD. Whereas research question b) is identical to research question 3 in Table 4, research

questions 1 and 2 are subquestions of the original research question a). The dossier submitted by the company describes the added benefit of ixekizumab in patients with active psoriatic arthritis who have responded inadequately to prior treatment with a DMARD; the company assumed these patients to be patients who are candidates for treatment with a bDMARD for the first time (research question 2). It chose adalimumab as ACT. These documents have remained relevant also after the G-BA changed patient groups and ACT; however, it was checked in the benefit assessment whether the relevant studies included patients that should be allocated to research question 1. The company determined no ACT for research question 1 or for research question 3.

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: patients with active psoriatic arthritis without poor prognostic factors

2.3.1 Information retrieval and study pool

Not applicable as the company did not investigate research question 1 in its dossier.

2.3.2 Results on added benefit

In its dossier, the company presented no data for the assessment of the added benefit of ixekizumab in comparison with the ACT for patients with active psoriatic arthritis without poor prognostic factors. This resulted in no hint of an added benefit of ixekizumab in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

An added benefit is not proven because the company presented no data for the assessment of the added benefit of ixekizumab in comparison with the ACT for patients with active psoriatic arthritis without poor prognostic factors.

2.3.4 List of included studies

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

2.4 Research question 2: patients with active psoriatic arthritis who are candidates for treatment with a bDMARD for the first time

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 ixekizumab (status: 10 January 2018)
- bibliographical literature search on ixekizumab (last search on 27 November 2017)
- search in trial registries for studies on ixekizumab (last search on 28 November 2017)

To check the completeness of the study pool:

- search in trial registries for studies on ixekizumab (last search on 7 March 2018)

The check identified no additional relevant study.

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: ixekizumab vs. adalimumab

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
RHAP	Yes	Yes	No
a: Study sponsored by the company. RCT: randomized controlled trial; vs.: versus			

Section 2.4.4 contains a reference list for the studies included.

2.4.1.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison: ixekizumab vs. adalimumab

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
RHAP	RCT, double-blind, parallel	Adult patients with active PsA who have not yet received treatment with a bDMARD	Ixekizumab Q4W (N = 107) ixekizumab Q2W (N = 103)[b] adalimumab (N = 101) placebo (N = 106)[b] Relevant subpopulation thereof[c]: ixekizumab Q4W: n = 51 adalimumab: n = 56	Screening: up to 30 days Treatment: 24 weeks (+ optional extension phase with ixekizumab for 28 weeks) Observation: at least 12 weeks after the end of treatment or optional longterm extension phase	114 centres in Belgium, Bulgaria, Canada, Czech Republic, Estonia, France, Japan, Mexico, Netherlands, Poland, Russia, Spain, Ukraine, United Kingdom, USA 1/2013–ongoing Database closure for the 24-week analysis: 26 Feb 2015	Primary: improvement in joint symptoms (ACR20) Secondary: disease activity, symptoms, health status, 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 relevant available outcomes for this benefit assessment.
b: The arm is not relevant for the assessment and is no longer shown in the next tables.
c: Patients with inadequate response or intolerance to one of several csDMARDs and without associated moderate to severe psoriasis (PASI ≤ 10 and BSA ≤ 10) (see text for explanations).

ACR20: 20% improvement in American College of Rheumatology criteria; AE: adverse event; bDMARD: biologic disease-modifying antirheumatic drug; BSA: affected body surface area; csDMARD: conventional synthetic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; n: relevant subpopulation; N: number of randomized patients; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis; Q2W: every 2 weeks; Q4W: every 4 weeks; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: ixekizumab vs. adalimumab

Study	Intervention	Comparison
RHAP	Ixekizumab SC week 0: 80 mg twice week 2–24: 80 mg once every 4 weeks (weeks 4, 8, 12 etc.) + placebo for adalimumab every 4 weeks (weeks 0, 2, 6, 10 etc.) in case of inadequate response[a] at week 16: administration of rescue therapy[b] and continuation of ixekizumab treatment until week 24	Adalimumab SC week 0: 40 mg once week 2–24: 40 mg once every 2 weeks + placebo for ixekizumab every 4 weeks (weeks 0, 4, 8, 12 etc.) in case of inadequate response[a] at week 16: administration of rescue therapy[b] and discontinuation of adalimumab and wash-out phase with placebo until week 24
	Pretreatment: not allowed: ▪ bDMARD treatment for PsA or biologic therapy for psoriasis ▪ parenteral glucocorticoids within 6 weeks before randomization ▪ opiate analgesics (> 30 mg morphine or equivalent) within 6 weeks before randomization ▪ systemic psoriasis treatment (except methotrexate, corticosteroids or phototherapy) within 4 weeks before randomization or topical psoriasis treatment within 2 weeks before randomization ▪ natalizumab or other alpha-4 integrin inhibitors ▪ csDMARDs other than methotrexate, leflunomide, sulfasalazine or hydroxychloroquine within 8 weeks before randomization **Concomitant treatment** ▪ NSAIDs, COX-2 inhibitors, maintained stable dose, adjustments only in the framework of the rescue therapy, csDMARDs (methotrexate, leflunomide, sulfasalazine or hydroxychloroquine): stable dose before study start maintained ▪ oral corticosteroids (< 10 mg/day prednisone or equivalent), stable dose within 4 weeks before baseline maintained ▪ mild topical corticosteroids (for face, armpits or genital area) ▪ the combination of methotrexate + leflunomide was not allowed for safety reasons	

a: Defined as 20% decrease in tender and swollen joint count.
b: Restricted to adjustments of the NSAID, opiate, DMARD, or oral corticosteroid doses or use of another DMARD. At most 1 intraarticular corticosteroid injection per year was allowed.
bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; COX: cyclooxygenase; csDMARD: conventional synthetic disease-modifying antirheumatic drug; NSAID: nonsteroidal anti-inflammatory drug; PsA: psoriatic arthritis; RCT: randomized controlled trial; SC: subcutaneous; vs.: versus

Description of the study design

The RHAP study was a randomized, double-blind, active-controlled parallel group study. The relevant study arms compared ixekizumab with adalimumab. The study included patients with active psoriatic arthritis, defined according to the Classification for Psoriatic Arthritis (CASPAR) criteria [4]. In addition, patients had to have at least 3/68 tender joints and 3/66 swollen joints. There had to be at least 1 disease-related radiographic joint damage of the hand or foot joints or a C-reactive protein (CRP) value of > 6 mg/L, and patients had to have active

psoriatic skin lesions or a personal history of plaque psoriasis. Hence, the study did not include any patients without poor prognostic factors who would have been allocated to research question 1. The patients had to present with established diagnosis of active psoriatic arthritis for at least 6 months. The study included treatment-naive patients and patients pretreated with conventional synthetic DMARDs (csDMARDs). Pretreatment with a bDMARD was not allowed.

A total of 208 patients were randomized to the relevant study arms and allocated to treatment with ixekizumab (N = 107) or adalimumab (N = 101). Randomization was stratified by country and pretreatment with a csDMARD (csDMARD-naive, pretreated or current csDMARD treatment). A double-dummy design ensured blinding.

The patients were treated in compliance with the regimen described in Table 7. Concomitant treatment with a csDMARD (methotrexate, leflunomide, sulfasalazine or hydroxychloroquine) while maintaining the stable dose used before study start was allowed. This deviates from the approval of ixekizumab insofar as ixekizumab is approved only alone or in combination with methotrexate. This had not relevance for the benefit assessment as the proportion of patients who received a csDMARD other than methotrexate was markedly below 20% in the relevant subpopulation of the RHAP study. Apart from this deviation, treatment in the study was in compliance with the SPCs of ixekizumab and adalimumab [5,6]. The treatment duration was 24 weeks; the patients could then participate in a voluntary extension phase. Patients from the ixekizumab arm continued treatment with ixekizumab, and patients from the adalimumab arm could switch to treatment with ixekizumab after an 8-week wash-out phase. The follow-up period for all patients was at least 12 weeks.

Patients with only inadequate response at treatment week 16 (defined as < 20% decrease in tender and swollen joint count) were to receive rescue therapy. This was restricted to modifications of the concomitant medications allowed in the study (see Table 7). Patients in the ixekizumab arm with an inadequate response received rescue medication in addition to continued ixekizumab treatment. Patients in the adalimumab arm were switched to placebo and received only rescue medication; after week 24 they could be switched to treatment with ixekizumab in the framework of the extension phase. Patients with an inadequate response at treatment week 16 who received rescue medication were rated as non-responders for the outcomes on morbidity and health-related quality of life from this time point.

Primary outcome of the study was the ACR20. Secondary outcomes were disease activity, symptoms, health status, health-related quality of life, and AEs.

The RHAP study is still ongoing. The assessment was based on the predefined data cut-off of the 24-week analysis from 26 February 2015.

Subpopulation relevant for research question 2

The subpopulation relevant for research question 2 comprised patients with active psoriatic arthritis who are candidates for treatment with a bDMARD for the first time. According to the SPC of ixekizumab, the patients had to have responded inadequately to, or have not tolerated prior treatment with a DMARD [6]. However, the RHAP study also included patients without prior DMARD treatment. In addition, the 4-week dosing interval administered in the relevant ixekizumab arm of the RHAP study is only approved for patients without concomitant moderate to severe plaque psoriasis (treatment regimen for moderate to severe plaque psoriasis: In the first 12 weeks ixekizumab every 2 weeks, then every 4 weeks). Patients with moderate to severe plaque psoriasis were also included in the study.

The company presented analyses of a subpopulation that, on the one hand, comprised only patients with DMARD pretreatment and, on the other, excluded patients with moderate to severe plaque psoriasis (defined as PASI > 10 and body surface area [BSA] > 10%). The patients included in the subpopulation presented by the company (N = 51 in the ixekizumab arm and N = 56 in the adalimumab arm) were treated in compliance with the SPC of ixekizumab and were the basis for the present benefit assessment. However, only conclusions for patients without concomitant moderate to severe plaque psoriasis can be derived on the basis of this subpopulation. The company presented no data for patients with psoriatic arthritis and moderate to severe plaque psoriasis.

Characteristics of the patient population

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

Table 8: Characteristics of the study populations – RCT, direct comparison: ixekizumab vs. adalimumab

Study Characteristics Category	Ixekizumab	Adalimumab
RHAP	N[a] = 51	N[a] = 56
Age [years], mean (SD)	50 (11)	48 (11)
Sex [F/M], %	65/35	59/41
Ethnic origin, n (%)		
White	48 (94.1)	53 (94.6)
Other	3 (5.9[b])	3 (5.4[b])
Time since diagnosis [years], mean (SD)	11.1 (11.2)	7.9 (6.0)
DAS 28 [CRP] score, mean (SD)	4.8 (1.1)	4.8 (1.0)
PASI score, mean (SD)	3.3 (2.5)	2.6 (2.4)
LEI > 0, n (%)	31 (60.8)	27 (48.2)
LDI-B > 0, n (%)	17 (33.3)	9 (16.1)
BSA ≥ 3%, n (%)	25 (49.0)	29 (51.8)
NAPSI > 0, n (%)	26 (51.0)	37 (66.1)
Treatment discontinuation, n (%)	7 (13.7[b])	1 (1.8[b])
Study discontinuation, n (%)	ND	ND

a: Number of randomized patients in the relevant subpopulation.
b: Institute's calculation.

BSA: body surface area; CRP: C-reactive protein; DAS: Disease Activity Score; F: female; LDI-B: Leeds Dactylitis Index-Basic; LEI: Leeds Enthesitis Index; M: male; n: number of patients in the category; N: number of randomized patients; NAPSI: Nail Psoriasis Severity Index; ND: no data; RCT: randomized controlled trial; SD: standard deviation; s.: versus

The patient characteristics were largely balanced between the treatment groups. The mean age of the patients in the relevant subpopulation was 49 years, about 60% were female and over 90% were white. It was noteworthy, however, that the proportion of patients with dactylitis was about twice as high in the ixekizumab arm (about 33%) as in the adalimumab arm (about 16%). The proportion of study discontinuations was notably higher in the ixekizumab arm (about 14%) than in the adalimumab arm (just under 2%). The proportion of patients with inadequate response at treatment week 16 (see above) was almost the same in both study arms (ixekizumab arm 4 [7.8%] and adalimumab arm 5 [8.9%]).

Risk of bias at study level

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: ixekizumab vs. adalimumab

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			
RHAP	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

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

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - minimal disease activity (MDA_{PASI})
  - physical functioning (HAQ-DI)
  - enthesitis (LEI)
  - dactylitis (LDI-B)
  - nail psoriasis (NAPSI)
  - skin symptoms (PASI 100)
  - health status (EQ-5D VAS)
  - joint pain (PAP VAS)
  - patient-reported global disease activity (PatGA VAS)
  - fatigue (Fatigue Severity NRS)
  - disease activity of ankylosing spondylitis (BASDAI)
  - tender/swollen joint count
- Health-related quality of life

- generic health-related quality of life (SF-36)
- disease-specific health-related quality of life (DLQI)

- Side effects
  - SAEs
  - discontinuation due to AEs
  - infections and infestations
  - general disorders and administration site conditions
  - 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) (see Section 2.7.2.4.3 of the full dossier assessment).

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

Table 10: Matrix of outcomes – RCT, direct comparison: ixekizumab vs. adalimumab

Study	Outcomes																	
	All-cause mortality	**Minimal disease activity (MDA_{PASI})**	**Physical functioning (HAQ-DI)**	**Enthesitis (LEI)**	**Dactylitis (LDI-B)**	**Nail psoriasis (NAPSI)**	**Skin symptoms (PASI 100)**	**Health status (EQ-5D VAS)**	**Joint pain (PAP VAS)**	**Patient-reported global disease activity (PatGA VAS)**	**Fatigue (Fatigue Severity NRS)**	**Disease activity of ankylosing spondylitis (BASDAI)**	**Tender/swollen joint count**	**Health-related quality of life (SF-36)**	**Health-related quality of life (DLQI)**	**SAEs**	**Discontinuation due to AEs**	**Further specific AEs[a]**
RHAP	Y	Y	Y	Y	Y	N[b]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

a: The following events (MedDRA coding) are considered: “general disorders and administration site conditions (SOC, AE)”, “infections and infestations (SOC, SAE)”.
b: No usable data (see Section 2.7.2.4.3 of the full dossier assessment).

AE: adverse event; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life-5 Dimensions; HAQ-DI: Health Assessment Questionnaire-Disability Index; LDI-B: Leeds Dactylitis Index-Basic; LEI: Leeds Enthesitis Index; MDA: minimal disease activity; MedDRA: Medical Dictionary for Regulatory Activities; N: no; NAPSI: Nail Psoriasis Severity Index; NRS: numeric rating scale; PAP: Patient Assessment of Pain; PASI: Psoriasis Area and Severity Index; PatGA: Patient Global Assessment of Disease Activity; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus; Y: yes

2.4.2.2 Risk of bias

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

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: ixekizumab vs. adalimumab

Study	Study level	Outcomes																	
		All-cause mortality	Minimal disease activity (MDA_{PASI})	Physical functioning (HAQ-DI)	Enthesitis (LEI)	Dactylitis (LDI-B)	Nail psoriasis (NAPSI)	Skin symptoms (PASI 100)	Health status (EQ-5D VAS)	Joint pain (PAP VAS)	Patient-reported global disease activity (PatGA VAS)	Fatigue (Fatigue Severity NRS)	Disease activity of ankylosing spondylitis (BASDAI)	Tender/swollen joint count	Health-related quality of life (SF-36)	Health-related quality of life (DLQI)	SAEs	Discontinuation due to AEs	Further specific AEs[a]
RHAP	L	L	H[b]	H[b]	L	L	-[c]	H[b]	L	L	L	L	L	L	L	H[b]	L	L	L

a: The following events (MedDRA coding) are considered: "general disorders and administration site conditions (SOC, AE)", "infections and infestations (SOC, SAE)".
b: Unknown proportion of imputed values.
c: No usable data.

AE: adverse event; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life-5 Dimensions; H: high; HAQ-DI: Health Assessment Questionnaire-Disability Index; L: low; LDI-B: Leeds Dactylitis Index-Basic; LEI: Leeds Enthesitis Index; MDA: minimal disease activity; MedDRA: Medical Dictionary for Regulatory Activities; NAPSI: Nail Psoriasis Severity Index; NRS: numeric rating scale; PAP: Patient Assessment of Pain; PASI: Psoriasis Area and Severity Index; PatGA: Patient Global Assessment of Disease Activity; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The risk of bias was rated as low for all outcomes for which usable data were available, except for the following outcomes: minimal disease activity (MDA_{PASI}), HAQ-DI, PASI 100, and DLQI.

The risk of bias of the outcome "MDA_{PASI}" was rated as high because of the unknown proportion of imputed values in the analysis. The number of patients imputed as non-responders was unclear for the outcomes "HAQ-DI" and "DLQI". Hence, the risk of bias of these outcomes was also rated as high. The proportion of imputed values was unclear for the outcome "PASI 100", which was therefore also rated as potentially highly biased (see also Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment for reasons).

The assessment deviates from that of the company insofar as the company rated the risk of bias as low for all outcomes it included.

2.4.2.3 Results

Table 12 and Table 13 summarize the results on the comparison of ixekizumab with adalimumab in patients with active psoriatic arthritis who are candidates for treatment with a bDMARD for the first time. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Tables with the common AEs can be found in Appendix A of the full dossier assessment.

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: ixekizumab vs. adalimumab

Study Outcome category Outcome	Ixekizumab		Adalimumab		Ixekizumab vs. adalimumab
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value[b]
RHAP					
Mortality					
All-cause mortality	51	0 (0)	56	0 (0)	–
Morbidity					
Minimal disease activity (MDA_{PASI})[c]	51	18 (35.3)	56	19 (33.9)	1.04 [0.62; 1.75]; 0.921
Physical functioning (HAQ-DI improvement ≥ 0.35)	51	24 (47.1)	56	27 (48.2)	0.98 [0.66; 1.45]; 0.947
Nail psoriasis – absence of symptoms (NAPSI = 0)				No usable data	
Skin symptoms					
Remission (PASI 100)	51	22 (43.1)	56	12 (21.4)	2.01 [1.11; 3.64]; 0.016
PASI 90 (additional information)	*51*	*27 (52.9)*	*56*	*14 (25.0)*	*2.12 [1.26; 3.57]; 0.003*
PASI 75 (additional information)	*51*	*31 (60.8)*	*56*	*20 (35.7)*	*1.70 [1.12; 2.58]; 0.010*
Health-related quality of life					
DLQI (0 or 1)	51	32 (62.7)	56	30 (53.6)	1.17 [0.85; 1.62]; 0.365
Side effects					
AEs (additional information)	51	35 (68.6)	56	36 (64.3)	–
SAEs	51	4 (7.8)	56	4 (7.1)	1.10 [0.29; 4.16]; 0.947
Discontinuation due to AEs	51	1 (2.0)	56	0 (0.0)	3.29 [0.14; 78.96][d]; 0.359
General disorders and administration site conditions	51	17 (33.3)	56	6 (10.7)	3.11 [1.33; 7.28]; 0.004
Infections and infestations	51	12 (23.5)	56	13 (23.2)	1.01 [0.51; 2.01]; > 0.999

(continued)

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: ixekizumab vs. adalimumab (continued)

a: Patients with missing values were imputed as non-responders in analyses for morbidity outcomes. The proportion of imputed values is unknown.
b: Institute's calculation (unconditional exact test, CSZ method according to [7]).
c: At least 5 of the following criteria have to be met to be rated as MDA_{PASI} responder:
- TJC (68) ≤ 1
- SJC (66) ≤ 1
- PASI score ≤ 1 or BSA ≤ 3%
- PAP VAS score ≤ 15 mm
- PatGA VAS score ≤ 20 mm
- HAQ-DI score ≤ 0.5
- LEI score ≤ 1

d: Since no event occurred in the adalimumab arm, the correction factor of 0.5 was used in the calculation of effect and CI (addition of 0.5 to each cell frequency).

AE: adverse event; BSA: body surface area; CI: confidence interval; CSZ: convexity, symmetry, z score; DLQI: Dermatology Life Quality Index; HAQ-DI: Health Assessment Questionnaire-Disability Index; LEI: Leeds Enthesitis Index; MDA: minimal disease activity; n: number of patients with (at least one) event; N: number of analysed patients; NAPSI: Nail Psoriasis Severity Index; PAP: Patient Assessment of Pain; PASI: Psoriasis Severity Index; PatGA: Patient Global Assessment of Disease Activity; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SJC: swollen joint count; TJC: tender joint count; VAS: visual analogue scale; vs.: versus

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

Study Outcome category Outcome	Ixekizumab			Adalimumab			Ixekizumab vs. adalimumab
	N[a]	Values at study start mean (SD)	Change at end of study mean (SE)[b]	N[a]	Values at study start mean (SD)	Change at end of study mean (SE)[b]	MD [95% CI]; p-value[b]
RHAP							
Morbidity							
Enthesitis (LEI)[c]	ND	1.4 (1.68)	−0.97 (0.19)	ND	1.5 (1.90)	−0.29 (0.20)	−0.68 [−1.15; −0.21]; 0.005
Dactylitis (LDI-B)[c]	ND	23.5 (57.01)	−17.18 (0.54)	ND	14.8 (43.10)	−17.61 (0.55)	−0.43 [−0.84; 1.71]; 0.502
Health status (EQ-5D VAS)[d]	ND	58.42 (20.38)	10.67 (3.14)	ND	58.20 (19.48)	11.86 (3.13)	−1.19 [−8.85; 6.47]; 0.759
Joint pain (PAP VAS)[c]	ND	53.31 (20.73)	−28.92 (3.42)	ND	57.31 (20.33)	−28.16 (3.37)	−0.76 [−9.35; 7.84]; 0.861
Patient-reported global disease activity (PatGA VAS)[c]	ND	57.45 (21.40)	−35.64 (3.29)	ND	58.76 (20.19)	−30.50 (3.25)	5.15 [−13.32; 3.03]; 0.214
Fatigue (Fatigue Severity NRS)[c]	ND	5.53 (2.39)	−1.71 (0.33)	ND	5.11 (2.64)	−1.25 (0.33)	−0.46 [−1.27; 0.35]; 0.263
Disease activity of ankylosing spondylitis (BASDAI)[c]	ND	5.41 (1.81)	−2.30 (0.31)	ND	5.29 (2.15)	−1.89 (0.30)	−0.41 [−1.16; 0.33]; 0.274
Tender joint count[c]	ND	19.00 (13.10)	−13.96 (1.19)	ND	17.54 (12.88)	−10.80 (1.17)	−3.16 [−6.07; −0.26]; 0.034
Swollen joint count[c]	ND	10.61 (7.97)	−7.87 (0.55)	ND	9.30 (6.48)	−6.22 (0.55)	−1.64 [−2.99; −0.30]; 0.017
Health-related quality of life							
SF-36 PCS[d]	ND	33.0 (10.02)	7.40 (1.32)	ND	34.2 (9.37)	5.67 (1.31)	1.73 [−1.43; 4.89]; 0.281
General health perception	ND	14.2 (3.38)	2.02 (0.50)	ND	14.1 (3.74)	2.34 (0.50)	−0.32 [−1.51; 0.87]; 0.593
Physical functioning	ND	18.5 (4.88)	3.73 (0.67)	ND	19.6 (5.26)	2.37 (0.66)	1.35 [−0.26; 2.96]; 0.099
Physical role functioning	ND	11.3 (4.27)	3.20 (0.56)	ND	11.4 (3.97)	2.46 (0.56)	0.74 [−0.61; 2.09]; 0.278
Bodily pain	ND	6.0 (1.94)	2.02 (0.33)	ND	6.1 (1.83)	1.74 (0.33)	0.28 [−0.53; 1.09]; 0.495

(continued)

Table 13: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ixekizumab vs. adalimumab (continued)

Study Outcome category	Ixekizumab			Adalimumab			Ixekizumab vs. adalimumab
Outcome	N[a]	Values at study start mean (SD)	Change at end of study mean (SE)[b]	N[a]	Values at study start mean (SD)	Change at end of study mean (SE)[b]	MD [95% CI]; p-value[b]
SF-36 MCS[d]	ND	47.7 (12.28)	5.56 (1.25)	ND	46.5 (11.25)	5.92 (1.24)	−0.35 [−3.33; 2.63]; 0.816
Emotional role functioning	ND	11.9 (2.64)	1.62 (0.27)	ND	11.8 (2.86)	1.61 (0.27)	0.01 [−0.63; 0.65]; 0.975
Mental wellbeing	ND	18.0 (4.44)	2.37 (0.49)	ND	17.9 (4.16)	2.17 (0.49)	0.19 [−0.98; 1.37]; 0.747
Social functioning	ND	7.4 (2.01)	1.38 (0.22)	ND	7.2 (2.10)	1.33 (0.22)	0.05 [−0.47; 0.56]; 0.857
Vitality	ND	10.8 (3.45)	1.95 (0.55)	ND	10.7 (3.58)	1.79 (0.54)	0.16 [−1.17; 1.49]; 0.814

a: There is no information on the number of patients included in the respective analysis. It can be inferred, however, that the proportion of patients who were not considered in the analysis was below 15% in each treatment arm; see Section 2.4.2.2.
b: Changes at the end of study in comparison with baseline and mean differences from MMRM analysis of the ITT population. The model contained terms for treatment, visit, geographical region and csDMARD experience, the baseline value as covariate and visit by treatment interaction.
c: Negative changes indicate improvement; a negative mean difference indicates an advantage of ixekizumab.
d: Positive change in the course of the study indicates improvement, a positive mean difference indicates an advantage of the test intervention.

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CI: confidence interval; csDMARD: conventional synthetic disease-modifying antirheumatic drug; EQ-5D: European Quality of Life-5 Dimensions; ITT: intention to treat; LDI-B: Leeds Dactylitis Index-Basic; LEI: Leeds Enthesitis Index; MCS: Mental Component Summary; MMRM: mixed-effects model repeated measures; N: number of analysed patients; ND: no data; NRS: numeric rating scale; PAP: Patient Assessment of Pain; PatGA: Patient Global Assessment of Disease Activity; PCS: Physical Component Summary; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SF-36: Short Form (36) Health Survey; VAS: visual analogue scale; s: versus

Based on the available data, at most hints, e.g. of an added benefit, can be determined for the outcomes "MDA_{PASI}", "HAQ-DI", "PASI 100" and "DLQI" because of the high risk of bias, and at most indications for all other outcomes.

Mortality

All-cause mortality

No death occurred in the relevant subpopulation during the study period. This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Minimal disease activity (MDA_{PASI})

No statistically significant difference between the treatment groups was shown for the outcome "minimal disease activity" recorded with the MDA_{PASI}. This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Physical functioning (HAQ-DI)

No statistically significant difference between the treatment groups was shown for the outcome "physical functioning" recorded with the HAQ-DI. This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Enthesitis (LEI)

For the outcome "enthesitis (LEI)", a statistically significant difference in favour of ixekizumab was shown regarding the change from baseline in the number of tender entheses. The 95% CI of the effect was [0.21; 1.15] entheses. The relevance of this effect cannot be estimated with certainty. For this reason, the certainty of the result was downgraded for this outcome. This resulted in a hint of an added benefit of ixekizumab in comparison with adalimumab for the outcome "enthesitis".

This contradicts the assessment of the company, which derived an indication of an added benefit based on the proportion of patients with a LEI of 0 at week 24. However, only patients with enthesitis at baseline were included in the analyses used by the company.

Dactylitis (LDI-B)

No statistically significant difference between the treatment groups was shown for the outcome "dactylitis" recorded with the LDI-B. This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Nail psoriasis (NAPSI)

There were no usable data for the outcome "nail psoriasis" recorded with the NAPSI (see Section 2.7.2.4.3 of the full dossier assessment). This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Skin symptoms (PASI 100)

A statistically significant difference in favour of ixekizumab was shown for the outcome "skin symptoms" recorded with the PASI 100. Due to the high risk of bias of the outcome, there was a hint of an added benefit of ixekizumab.

This deviates from the assessment of the company insofar as the company derived an indication of an added benefit.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for the outcome "health status" recorded with the EQ-5D VAS. This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Joint pain (PAP VAS)

There was no statistically significant difference between the treatment groups for the outcome "joint pain" recorded with the PAP VAS. This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Patient-reported global disease activity (PatGA VAS)

There was no statistically significant difference between the treatment groups for the outcome "patient-reported global disease activity" recorded with the PatGA VAS. This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Fatigue (Fatigue Severity NRS)

There was no statistically significant difference between the treatment groups for the outcome "fatigue" recorded with the Fatigue Severity NRS. This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Disease activity of ankylosing spondylitis (BASDAI)

No statistically significant difference between the treatment groups was shown for the outcome "disease activity of ankylosing spondylitis" recorded with the BASDAI. This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Tender joint count

For the outcome "tender joint count", a statistically significant difference in favour of ixekizumab was shown for the change from baseline. The 95% CI of the effect was [0.26; 6.07] joints. The relevance of this effect cannot be estimated with certainty. For this reason, the certainty of the result was downgraded for this outcome. This resulted in a hint of an added benefit of ixekizumab in comparison with adalimumab for the outcome "tender joint count".

This deviates from the assessment of the company, which derived no added benefit for this outcome.

Swollen joint count

For the outcome "swollen joint count", a statistically significant difference in favour of ixekizumab was shown for the change from baseline. The 95% CI of the effect was [0.30; 2.99] joints. The relevance of this effect cannot be estimated with certainty. For this reason, the certainty of the result was downgraded for this outcome. This resulted in a hint of an added benefit of ixekizumab in comparison with adalimumab for the outcome "swollen joint count".

This deviates from the assessment of the company, which derived no added benefit for this outcome.

Health-related quality of life

SF-36

For the SF-36, the MCS and the PCS were considered separately. In each case, there was no statistically significant difference between the treatment groups. In each case, this resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

DLQI

There was no statistically significant difference between the treatment groups for the outcome "DLQI". This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

Serious adverse events and discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". In each case, this resulted in no hint of lesser or greater harm of ixekizumab in comparison with adalimumab; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

General disorders and administration site conditions

A statistically significant difference to the disadvantage of ixekizumab was shown for the specific AE "general disorders and administration site conditions". This resulted in an indication of greater harm from ixekizumab.

This concurs with the assessment of the company insofar as the company derived lesser added benefit.

Infections and infestations

No statistically significant difference between the treatment groups was shown for the outcome "infections and infestations". This resulted in no hint of lesser or greater harm of ixekizumab in comparison with adalimumab; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

2.4.2.4 Subgroups and other effect modifiers

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

- sex (female/male)
- region (Europe/rest of the world)
- severity (CRP ≤ 6 mg/L versus > 6 mg/L)

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.

Table 14 shows the results of the subgroup analyses.

Table 14: Subgroups (morbidity) – RCT, direct comparison: ixekizumab vs. adalimumab

Study Outcome Characteristic Subgroup	Ixekizumab N	Ixekizumab Patients with event n (%)	Adalimumab N	Adalimumab Patients with event n (%)	Ixekizumab vs. adalimumab RR [95% CI]	Ixekizumab vs. adalimumab p-value
RHAP						
Minimal disease activity (MDA_{PASI})						
Geographical region						
Europe	37	10 (27.03)	44	16 (36.36)	0.74 [0.38; 1.44]	0.515[a]
Rest of the world	14	8 (57.14)	12	1 (8.33)	6.86 [0.99; 47.27]	0.011[a]
Total					Interaction:	0.033[b]

a: Institute's calculation (unconditional exact test, CSZ method according to [7]).
b: p-value from Q test for heterogeneity.
CI: confidence interval; CSZ: convexity, symmetry, z score; n: number of patients with (at least one) event; N: number of analysed patients; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Minimal disease activity (MDA_{PASI})

For the outcome "minimal disease activity" recorded with the MDA_{PASI}, an interaction by the characteristic "region" was shown for the relevant subpopulation. There was a statistically significant difference in favour of ixekizumab compared with adalimumab for patients from the region "rest of the world". There was no statistically significant difference between the treatment groups for patients from Europe. In the present constellation, the results from the region of Europe are relevant and were used for the benefit assessment. This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

The derivation of probability and extent of the added benefit is presented below at outcome level, 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 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 added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4.2.3 (see Table 15).

Determination of the outcome category for outcomes on symptoms and side effects

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

Main symptoms recorded with the PASI 100

The allocation of the outcome "remission" (PASI 100) to a particular outcome category (serious or non-serious) depends on the patients' initial situation, and particularly on the severity and the grade of impairment from the symptoms measured with PASI (psoriatic plaque redness, thickness and scaling).

The data recorded in the beginning of the study were used for assessing the severity of the symptoms. Patients with moderate to severe plaque psoriasis (PASI > 10 and BSA > 10) were excluded from the subpopulation of the RHAP study relevant for the assessment (see Section 2.4.1.2). The outcome was therefore assigned to the outcome category "non-serious/non-severe symptoms/late complications".

This deviates from the assessment of the company, which allocated the outcome to "serious/severe symptom/late complications".

Enthesitis, tender/swollen joint count

In the dossier, the company presented no information that allows an estimation of the severity category for the outcomes "enthesitis" and "tender/swollen joint count". The outcomes were therefore allocated to the category "non-serious/non-severe side effects".

This deviates from the assessment of the company, which allocated these outcomes to "serious/severe symptom/late complications".

General disorders and administration site conditions

The vast majority of the events for the outcome "general disorders and administration site conditions" in the subpopulation relevant for the assessment were non-serious. The outcome was therefore allocated to the category "non-serious/non-severe side effects".

This concurs with the company's assessment.

Determination of the extent of the added benefit for continuous outcomes

There were statistically significant results in favour of ixekizumab regarding the mean difference for each of the outcomes "enthesitis" and "tender/swollen joint count". The extent of the added benefit cannot be estimated with certainty. It was notable in the overall consideration of the results, however, that there were no statistically significant differences between the treatment groups for the patient-reported outcomes on joint pain, disease activity, physical functioning, health status, and also on health-related quality of life. Under the assumption that a more than minor improvement in the outcomes "enthesitis" and

"tender/swollen joint count" would have been reflected in at least some of the patient-reported outcomes mentioned, the extent of the added benefit is assessed as no more than "minor".

Table 15: Extent of added benefit at outcome level: ixekizumab vs. adalimumab

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ixekizumab vs. adalimumab** **Proportion of events (%) or mean change from study start to week 24** **Effect [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
Minimal disease activity Geographical region		
Europe	27.03% vs. 36.36% RR: 0.74 [0.38; 1.44]; p = 0.515	Lesser benefit/added benefit not proven
Physical functioning (HAQ-DI)	47.1% vs. 48.2% RR: 0.98 [0.66; 1.45]; p = 0.947	Lesser benefit/added benefit not proven
Enthesitis (LEI)	−0.97 vs. −0.29 MD: −0.68 [−1.15; −0.21]; p = 0.005 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "minor"
Dactylitis (LDI-B)	−17.18 vs. −17.61 MD: −0.43 [−0.84; 1.71]; p = 0.502	Lesser benefit/added benefit not proven
Nail psoriasis – absence of symptoms (NAPSI)[c]	No usable data	Lesser benefit/added benefit not proven
Skin symptoms remission (PASI 100)	43.1% vs. 21.4% RR: 2.01 [1.11; 3.64]; p = 0.016 RR: 0.50 [0.27; 0.898][d] Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.90$ Added benefit, extent: "minor"
Health status (EQ-5D VAS)	10.67 vs. 11.86 MD: −1.19 [−8.85; 6.47]; p = 0.759	Lesser benefit/added benefit not proven
Joint pain (PAP VAS)	−28.92 vs. −28.16 MD: −0.76 [−9.35; 7.84]; p = 0.861	Lesser benefit/added benefit not proven
Patient-reported global disease activity (VAS)	−35.64 vs. −30.50 MD: 5.15 [−13.32; 3.03]; p = 0.214	Lesser benefit/added benefit not proven
Fatigue (NRS)	−1.71 vs. −1.25 MD: −0.46 [−1.27; 0.35]; p = 0.263	Lesser benefit/added benefit not proven
Disease activity of ankylosing spondylitis (BASDAI)	−2.3 vs. −1.89 MD: −0.41 [−1.16; 0.33]; p = 0.274	Lesser benefit/added benefit not proven
Tender joint count	−13.96 vs. −10.80 MD: −3.16 [−6.07; −0.26]; p = 0.034 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "minor"

(continued)

Table 15: Extent of added benefit at outcome level: ixekizumab vs. adalimumab (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ixekizumab vs. adalimumab** **Proportion of events (%) or mean change from study start to week 24** **Effect [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Swollen joint count	−7.87 vs. −6.22 MD: −1.64 [−2.99; −0.30]; p = 0.017 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "minor"
Health-related quality of life		
DLQI (0 or 1)	62.7% vs. 53.6% RR: 1.17 [0.85; 1.62]; p = 0.365	Lesser benefit/added benefit not proven
SF-36		
Physical sum score	7.40 vs. 5.67 MD: 1.73 [−1.43; 4.89]; p = 0.281	Lesser benefit/added benefit not proven
Mental sum score	5.56 vs. 5.92 MD: −0.35 [−3.33; 2.63]; p = 0.816	Lesser benefit/added benefit not proven
Side effects		
SAEs	7.8% vs. 7.1% RR: 1.10 [0.29; 4.16]; p = 0.947	Greater/lesser harm not proven
Discontinuation due to AEs	2% vs. 0% RR: 3.29 [0.14; 78.96]; p = 0.359	Greater/lesser harm not proven
General disorders and administration site conditions	33.3% vs. 10.7% RR: 3.11 [1.33; 7.28]; p = 0.004 RR: 0.32 [0.14; 0.75][d] Probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"
Infections and infestations	23.5% vs. 23.2% RR: 1.01 [0.51; 2.01]; p > 0.999	Greater/lesser harm not proven

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: The analysis includes only patients with nail psoriasis at the start of the study.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
h: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
AE: adverse event; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CI: confidence interval; CI_u: upper limit of confidence interval; HAQ-DI: Health Assessment Questionnaire-Disability Index; LDI-B: Leeds Dactylitis Index-Basic; LEI: Leeds Enthesitis Index; MD: mean difference; NRS: numeric rating scale; OR: odds ratio; PAP: Patient Assessment of Pain; PASI: Psoriasis Area and Severity Index; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.3.2 Overall conclusion on added benefit

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

Table 16: Positive and negative effects from the assessment of ixekizumab in comparison with adalimumab

Positive effects	**Negative effects**
Outcome category: non-serious/non-severe symptoms/late complications ▪ skin symptoms (PASI 100): hint of an added benefit – extent: "minor" ▪ enthesitis: hint of an added benefit – extent "minor" ▪ tender/swollen joint count: in each case hint of an added benefit – extent "minor"	Outcome category: non-serious/non-severe side effects ▪ specific AEs (general disorders and administration site conditions): indication of greater harm – extent "considerable"
AE: adverse event; PASI: Psoriasis Area and Severity Index	

The overall consideration showed several hints with the extent "minor" on the side of positive effects. These were accompanied by an indication of greater harm with the extent "considerable" on the side of negative effects. This did not completely outweigh the positive effects, however.

In summary, there is a hint of a minor added benefit for bDMARD-naive patients with active psoriatic arthritis for whom a first treatment with bDMARDs is indicated.

2.4.4 List of included studies

Eli Lilly and Company. A multicenter, randomized, double-blind, active and placebo-controlled 24-week study followed by long-term evaluation of efficacy and safety of ixekizumab (LY2439821) in biologic disease-modifying antirheumatic drug-naive patients with active psoriatic arthritis [online]. In: EU Clinical Trials Register. [Accessed: 19.03.2018]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-002326-49.

Eli Lilly and Company. A study of ixekizumab in participants with active psoriatic arthritis (SPIRIT-P1): study details [online]. In: ClinicalTrials.gov. 27.10.2017 [Accessed: 19.03.2018]. URL: https://ClinicalTrials.gov/show/NCT01695239.

Eli Lilly and Company. A study of ixekizumab in participants with active psoriatic arthritis (SPIRIT-P1): study results [online]. In: ClinicalTrials.gov. 27.10.2017 [Accessed: 19.03.2018]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01695239.

Mease PJ, Van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis 2017; 76(1): 79-87.

Eli Lilly and Company. A multicenter, randomized, double-blind, active and placebo-controlled 24-week study followed by long-term evaluation of efficacy and safety of ixekizumab (LY2439821) in biologic disease-modifying antirheumatic drug-naive patients with active psoriatic arthritis: study I1F-MC-RHAP; clinical study report [unpublished]. 2015.

Eli Lilly and Company. A multicenter, randomized, double-blind, active and placebo-controlled 24-week study followed by long-term evaluation of efficacy and safety of ixekizumab (LY2439821) in biologic disease-modifying antirheumatic drug-naive patients with active psoriatic arthritis: study I1F-MC-RHAP; Zusatzanalysen [unpublished]. 2018.

2.5 Research question 3: patients with active psoriatic arthritis who have responded inadequately to prior treatment with bDMARDs

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 ixekizumab (status: 10 January 2018)
- bibliographical literature search on ixekizumab (last search on 27 November 2017)
- search in trial registries for studies on ixekizumab (last search on 28 November 2017)

To check the completeness of the study pool:

- search in trial registries for studies on ixekizumab (last search on 7 March 2018)

Concurring with the company, the check of the completeness of the study pool produced no RCTs on the direct comparison of ixekizumab versus the ACT.

2.5.2 Results on added benefit

In its dossier, the company presented no data for the assessment of the added benefit of ixekizumab in comparison with the ACT for patients with active psoriatic arthritis who have responded inadequately to prior treatment with bDMARDs. This resulted in no hint of an added benefit of ixekizumab in comparison with the ACT; an added benefit is therefore not proven.

2.5.3 Probability and extent of added benefit

An added benefit is not proven because the company presented no data for the assessment of the added benefit of ixekizumab in comparison with the ACT for patients with active psoriatic arthritis who have responded inadequately to prior treatment with bDMARDs.

2.5.4 List of included studies

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

2.6 Probability and extent of added benefit – summary

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

Table 17: Ixekizumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Patients with active psoriatic arthritis without poor prognostic factors[b] who have responded inadequately to, or who have not tolerated prior treatment with a disease-modifying antirheumatic drug (conventional DMARDs, including methotrexate)	Alternative conventional DMARDs if suitable (methotrexate or leflunomide as monotherapy or combination therapy)	Added benefit not proven
2	bDMARD-naive patients with active psoriatic arthritis for whom a first treatment with bDMARDs is indicated	TNF alpha inhibitor (**adalimumab** or etanercept or golimumab or infliximab), if applicable in combination with methotrexate	Hint of minor added benefit[c]
3	Patients with active psoriatic arthritis who have responded inadequately to, or who have not tolerated prior treatment with bDMARDs	Switch to a different bDMARD (adalimumab or etanercept or golimumab or infliximab), if applicable in combination with methotrexate	Added benefit not proven

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: ≥ 5 affected joints; radiographic joint damage; increased inflammatory markers; extraarticular manifestations, particularly dactylitis.
c: Based on the data, a conclusion is only possible for patients without moderate to severe plaque psoriasis.
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

The assessment described above partly deviates from that of the company. Research question 1 was not investigated by the company; for research question 2, the company claimed an indication of considerable added benefit. For research question 3, the company considered the added benefit as not proven, which concurred with IQWiG.

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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