IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ixekizumab (plaque psoriasis) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Ixekizumab (Plaque Psoriasis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 May 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.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSA	body surface area
CI	confidence interval
DLQI	Dermatology Life Quality Index
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
NAPSI	Nail Psoriasis Severity Index
NB-UVB	narrowband ultraviolet B light (311 nm)
NRS	numeric rating scale
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
Peto OR	Peto odds ratio
PUVA	psoralen and ultraviolet-A light
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
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 27 February 2017.

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 adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy.

Two research questions resulted from this, for which the G-BA specified the ACTs presented in the following table.

Table 2: Research questions of the benefit assessment of ixekizumab

Research question	**Subindication**[a]	**ACT**[b]
A	Adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy[c]	**Fumaric acid esters** or ciclosporin or **methotrexate** or phototherapy (balneo-phototherapy, oral PUVA, NB-UVB)[d]
B	Adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or PUVA, or with contraindication or intolerance to such treatments	Adalimumab or infliximab or **ustekinumab**[d]

a: It is a precondition that only patients are treated for whom topical treatment alone is inadequate.
b: 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.
c: This population includes all patients in the approved therapeutic indication less the patients named in research question B.
d: Dosage of the ACT was to concur with the recommendations of the relevant SPCs. A dose-fair comparison under exhaustion of the approval-compliant dosage (if tolerated) was to be conducted.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); PUVA: psoralen and ultraviolet-A light; SPC: Summary of Product Characteristics

For easier presentation and better readability, the present benefit assessment uses the following terms for the 2 research questions:

- research question A: patients with plaque psoriasis who are candidates for systemic therapy

- research question B: patients with plaque psoriasis with inadequate response to other systemic treatments or who are unsuitable for these treatments

For research question A, the G-BA specified fumaric acid esters or ciclosporin or methotrexate or phototherapy (balneo-phototherapy, psoralen and ultraviolet-A light [PUVA], narrowband ultraviolet B light [NB-UVB]) as ACTs. The company followed these specifications and chose fumaric acid esters and methotrexate from the options mentioned. The company followed the G-BA's specifications also for research question B and chose ustekinumab from the options mentioned.

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. This concurs with the company's inclusion criteria.

Results for research question A: patients with plaque psoriasis who are candidates for systemic therapy

The company presented the study RHBZ for patients with plaque psoriasis who are candidates for systemic therapy. This study was principally suitable for answering the present research question. However, the results presented by the company, which were based on analyses of the total population, could not be used for the assessment of the added benefit of ixekizumab. This is explained below.

The RHBZ study was an RCT, which included patients with moderate to severe plaque psoriasis who had not yet received prior systemic treatment except phototherapy. The study had an open-label, 3-arm design. Patients in the intervention arm received ixekizumab and patients in the 2 comparator arms received either methotrexate or fumaric acid esters. The randomized study phase was 24 weeks.

In the RHBZ study, 40% of the patients had received phototherapy already before study inclusion. About 14% of the patients had received PUVA treatment, and about 22% had received UVB treatment. It was unclear for 6% of the patients which form of phototherapy they had received.

Since phototherapy is considered a type of systemic treatment, a large proportion of the patients had already received systemic pretreatment. For the present benefit assessment, however, it was assumed that the patients relevant to the research question had not yet received systemic treatment.

This assessment was reflected in the G-BA's justification regarding secukinumab. The therapeutic indications, the research questions and the ACTs of the present benefit assessment concur with those regarding the drug secukinumab. According to the G-BA's justification of the decision on secukinumab, the therapeutic indication on research question A comprises

patients who are candidates for systemic therapy, but have not yet received such treatment. In the ACT specified by the G-BA, phototherapy and other systemic treatments were presented as equivalent options for patients for whom topical treatment alone is inadequate. This also concurs with the recommendations of the German S3 guideline, which cites phototherapy as equivalent treatment option to conventional systemic treatments.

Regarding the patients in the methotrexate arm it should be noted that methotrexate is only approved for patients with the most severe forms of plaque psoriasis. The RHBZ study included patients with moderate to severe psoriasis. It was not clear from the data presented by the company that methotrexate was an appropriate treatment in compliance with the approval for all these patients.

There were no usable data for the assessment of the added benefit of ixekizumab in adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy. Hence there was no hint of an added benefit of ixekizumab in comparison with the ACT. An added benefit is therefore not proven.

Results for research question B: patients with plaque psoriasis with inadequate response to other systemic treatments or who are unsuitable for these treatments

One relevant study (IXORAS) was available for the benefit assessment.

Study pool and patient characteristics

The IXORAS study is a randomized, double-blind, parallel-group study currently conducted in 51 study centres worldwide. The study compares ixekizumab with ustekinumab in patients with moderate to severe plaque psoriasis with treatment failure, contraindication or intolerability to at least 1 systemic treatment (including methotrexate, ciclosporin or phototherapy). A Psoriasis Area and Severity Index (PASI) of ≥ 10 was used as inclusion criterion for the severity grade of the plaque psoriasis.

A total of 302 patients were randomly assigned to treatment with ixekizumab (N = 136) or ustekinumab (N = 166). Randomization of the patients was stratified by the factors body weight (≤ 100 kg versus > 100 kg) and study centre.

In each case, treatment was in compliance with the specifications of the Summaries of Product Characteristics (SPCs).

The primary outcome of the study is the proportion of patients with 90% reduction in PASI from baseline to week 12 (PASI 90). Secondary outcomes are remission (PASI 100), outcomes on symptoms and health-related quality of life, and side effects at week 12.

The study is still ongoing, and the present assessment was based on analyses of a planned interim analysis at week 24.

Risk of bias

The risk of bias was rated as low for all outcomes for which usable data were available. There were no usable data for the outcomes "no psoriasis symptoms in the facial, neck and genital area and on the fingernails".

Mortality

All-cause mortality

No deaths occurred in the IXORAS study up to treatment week 24. There was no hint of an added benefit of ixekizumab in comparison with ustekinumab; an added benefit is therefore not proven.

Morbidity

Remission (PASI 100)

A statistically significant difference in favour of ixekizumab was shown for the outcome "remission" (measured with the PASI 100). There was an indication of an added benefit of ixekizumab in comparison with ustekinumab.

Health-related quality of life

DLQI (0 or 1)

Regarding the proportion of patients who achieved a Dermatology Life Quality Index (DLQI) score of 0 or 1 at week 24, there was a statistically significant difference in favour of ixekizumab in comparison with ustekinumab. This resulted in an indication of an added benefit of ixekizumab in comparison with ustekinumab.

Side effects

No statistically significant difference between the treatment groups was shown for each of the following outcomes: serious adverse events (SAEs), discontinuation due to adverse events (AEs), and infections and infestations (recorded with the System Organ Class [SOC] of the standardized Medical Dictionary for Regulatory Activities [MedDRA]). Hence there was no hint of greater or lesser harm from ixekizumab for these outcomes; 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 outcome "general disorders and administration site conditions" (recorded with the SOC). This resulted in an indication of greater harm from ixekizumab in comparison with ustekinumab for this outcome.

Further outcomes

There were no usable data for the outcomes "no psoriasis symptoms in the facial, neck and genital area and on the fingernails".

There was no statistically significant and relevant difference between the treatment groups for each of the other following patient-relevant outcomes: itching, pain of skin, health status (recorded with the European Quality of Life-5 Dimensions questionnaire [EQ-5D]), health-related quality of life (recorded with the Short Form [36] Health Survey [SF-36]).

Hence there was no hint of an added benefit of ixekizumab for any these outcomes; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[4]

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:

In summary, the added benefit of ixekizumab is not proven for patients with plaque psoriasis who are candidates for systemic therapy (research question A).

In summary, there are both positive and negative effects of ixekizumab for patients with plaque psoriasis with inadequate response to other systemic treatments or who are unsuitable for these treatments (research question B). On the side of positive effects, there was an indication of considerable added benefit for the outcome category “morbidity” (remission [PASI 100]). For the outcome category “health-related quality of life”, there was an indication of a minor added benefit of ixekizumab in comparison with ustekinumab for the outcome “DLQI (0 or 1)”. The positive effects were accompanied by a negative effect in the category of non-serious/non-severe side effects. There was an indication of greater harm with the extent “considerable” for the outcome “general disorders and administration site conditions”. This did not challenge the positive effects of ixekizumab. In summary, there is an indication of considerable added benefit of ixekizumab in comparison with ustekinumab for this patient group.

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

[4] 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, no added benefit, or less benefit). For further details see [1,2].

Table 3: Ixekizumab – probability and extent of added benefit

Research question	Subindication[a]	ACT[b]	Probability and extent of added benefit
A	Adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy[c]	**Fumaric acid esters** or ciclosporin or **methotrexate** or phototherapy (balneo-phototherapy, oral PUVA, NB-UVB)[d]	Added benefit not proven
B	Adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or PUVA, or with contraindication or intolerance to such treatments	Adalimumab or infliximab or **ustekinumab**[d]	Indication of considerable added benefit

a: It is a precondition that only patients are treated for whom topical treatment alone is inadequate.
b: 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.
c: This population includes all patients in the approved therapeutic indication less the patients named in research question B.
d: Dosage of the ACT was to concur with the recommendations of the relevant SPCs. A dose-fair comparison under exhaustion of the approval-compliant dosage (if tolerated) was to be conducted.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); PUVA: psoralen and ultraviolet-A light; SPC: Summary of Product Characteristics

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

2.2 Research question

The aim of the present report was to assess the added benefit of ixekizumab in comparison with the ACT in adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy.

This resulted in 2 research questions, for which the G-BA specified the ACTs presented in Table 4.

Table 4: Research questions of the benefit assessment of ixekizumab

Research question	**Subindication**[a]	**ACT**[b]
A	Adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy[c]	**Fumaric acid esters** or ciclosporin or **methotrexate** or phototherapy (balneo-phototherapy, oral PUVA, NB-UVB)[d]
B	Adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or PUVA, or with contraindication or intolerance to such treatments	Adalimumab or infliximab or **ustekinumab**[d]

a: It is a precondition that only patients are treated for whom topical treatment alone is inadequate.
b: 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.
c: This population includes all patients in the approved therapeutic indication less the patients named in research question B.
d: Dosage of the ACT was to concur with the recommendations of the relevant SPCs. A dose-fair comparison under exhaustion of the approval-compliant dosage (if tolerated) was to be conducted.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); PUVA: psoralen and ultraviolet-A light; SPC: Summary of Product Characteristics

For easier presentation and better readability, the present benefit assessment uses the following terms for the 2 research questions:

- research question A: patients with plaque psoriasis who are candidates for systemic therapy
- research question B: patients with plaque psoriasis with inadequate response to other systemic treatments or who are unsuitable for these treatments

For research question A, the G-BA specified fumaric acid esters or ciclosporin or methotrexate or phototherapy (balneo-phototherapy, PUVA, NB-UVB) as ACTs. The company followed these specifications and chose fumaric acid esters and methotrexate from the options mentioned. The company followed the G-BA's specifications also for research question B and chose ustekinumab from the options mentioned.

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 A: patients with plaque psoriasis who are candidates for systemic therapy

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on ixekizumab (status: 23 December 2016)
- bibliographical literature search on ixekizumab (last search on 7 December 2016)
- search in trial registries for studies on ixekizumab (last search on 5 December 2016)

To check the completeness of the study pool:

- search in trial registries for studies on ixekizumab (last search on 7 March 2017)

No additional relevant study was identified from the check.

The company presented the study RHBZ for patients with plaque psoriasis who are candidates for systemic therapy. This study was principally suitable for answering the present research question. However, the results presented by the company, which were based on analyses of the total population, could not be used for the assessment of the added benefit of ixekizumab. This is explained below.

The RHBZ study was an RCT, which included patients with moderate to severe plaque psoriasis who had not yet received prior systemic treatment except phototherapy. The study had an open-label, 3-arm design. Patients in the intervention arm received ixekizumab and patients in the 2 comparator arms received either methotrexate or fumaric acid esters. The randomized study phase was 24 weeks.

In the RHBZ study, 40% of the patients had received phototherapy already before study inclusion. About 14% of the patients had received PUVA treatment, and about 22% had received UVB treatment. It was unclear for 6% of the patients which form of phototherapy they had received.

Since phototherapy is considered a type of systemic treatment [3], a large proportion of the patients had already received systemic pretreatment. For the present benefit assessment, however, it was assumed that the patients relevant to the research question had not yet received systemic treatment.

This assessment was reflected in the G-BA's justification regarding secukinumab [4]. The therapeutic indications, the research questions and the ACTs of the present benefit assessment concur with those regarding the drug secukinumab [5]. According to the G-BA's justification of the decision on secukinumab, the therapeutic indication on research question A comprises

patients who are candidates for systemic therapy, but have not yet received such treatment. In the ACT specified by the G-BA, phototherapy and other systemic treatments were presented as equivalent options for patients for whom topical treatment alone is inadequate [4]. This also concurs with the recommendations of the German S3 guideline, which cites phototherapy as equivalent treatment option to conventional systemic treatments [3].

Furthermore, in the RHBZ study, about half of the patients with prior phototherapy (20% of the total population) showed inadequate response to this treatment. In accordance with the research questions of the present benefit assessment, these patients possibly had to be allocated to research question B (patients with plaque psoriasis with inadequate response to other systemic treatments) and would not have been treated with the adequate ACT (adalimumab or infliximab or ustekinumab).

Regarding the patients in the methotrexate arm it should be noted that methotrexate is only approved for patients with the most severe forms of plaque psoriasis [6]. The RHBZ study included patients with moderate to severe psoriasis. It was not clear from the data presented by the company that methotrexate was an appropriate treatment in compliance with the approval for all these patients.

In summary, the results of the RHBZ study, which were based on analyses of the total population, were unsuitable for the assessment of the added benefit of ixekizumab. The main reason for this was that a large proportion of the patients had been pretreated with phototherapy.

The study and patient characteristics of the RHBZ study for research question A are presented in Appendix A of the full dossier assessment.

2.3.2 Results on added benefit

There were no usable data for the assessment of the added benefit of ixekizumab in adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy. Hence there was no hint of an added benefit of ixekizumab in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit

Since there were no relevant data for patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy, an added benefit is not proven.

2.4 Research question B: patients with plaque psoriasis with inadequate response to other systemic treatments or who are unsuitable for these treatments

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: 23 December 2016)
- bibliographical literature search on ixekizumab (last search on 7 December 2016)
- search in trial registries for studies on ixekizumab (last search on 5 December 2016)

To check the completeness of the study pool:

- search in trial registries for studies on ixekizumab (last search on 7 March 2017)

No additional relevant study was identified from the check.

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. ustekinumab

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Study RHBS (IXORAS[b])	No	Yes	No

a: Study for which the company was sponsor.
b: In the following tables, the study is referred to with this designation.
RCT: randomized controlled trial; vs.: versus

Section 2.4.4 contains a reference list for the study 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 study included – RCT, direct comparison: ixekizumab vs. ustekinumab

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
IXORAS	RCT, double-blind, parallel	Adult patients with moderate to severe plaque psoriasis (PASI ≥ 10) with treatment failure, contraindication or intolerability to at least 1 systemic treatment (including methotrexate, ciclosporin or phototherapy)	Ixekizumab (N = 136) ustekinumab (N = 166)	▪ Screening: up to 35 days ▪ Treatment: ▫ induction phase until week 12 ▫ maintenance phase: week 12 to 52 ▪ Extension phase: patients in the ixekizumab arm have the option to receive further 24 weeks of treatment	51 study centres in Austria, Belgium, Canada, France, Germany, Hungary, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, United Kingdom 10/2016–ongoing[b]	Primary: PASI 90 at week 12 Secondary: remission (PASI 100), symptoms, health-related quality of life, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Interim analyses at weeks 12 and 24.
AE: adverse event; N: number of randomized patients; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: ixekizumab vs. ustekinumab

Study	Intervention	Comparison	Prior and concomitant medication
IXORAS	**Induction phase:** ixekizumab SC ▪ week 0: 80 mg twice ▪ week 2 to 12: 80 mg once every 2 weeks placebo for ustekinumab in week 0 and 4 **Maintenance period:** ixekizumab SC 80 mg ▪ week 16 to 48: every 4 weeks placebo for ustekinumab in week 16, 28 and 40	**Induction phase:** ustekinumab SC ▪ week 0 and 4: 45 or 90 mg (depending on body weight: ≤ 100 kg = 45 mg, > 100 kg = 90 mg) placebo for ixekizumab in week 0 and in weeks 2 to 12 **Maintenance period:** ustekinumab SC ▪ week 16, 28 and 40: 45 or 90 mg (depending on body weight: ≤ 100 kg = 45 mg, > 100 kg = 90 mg) placebo for ixekizumab every 4 weeks in weeks 16 to 48	**Concomitant treatment permitted:** ▪ drug-free topical treatments, bath products, shampoos ▪ NSAIDs, acetaminophen, aspirin **Concomitant medication prohibited:** ▪ drug-containing urea (> 3% salicylic acid or corticosteroids), topical treatments ▪ other systemic psoriasis treatments (including phototherapy) ▪ corticosteroids ▪ live vaccines ▪ BCG vaccination

BCG: bacille Calmette-Guérin; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; SC: subcutaneous; vs.: versus

The IXORAS study is a randomized, double-blind, parallel-group study currently conducted in 51 study centres worldwide. The study compares ixekizumab with ustekinumab in patients with moderate to severe plaque psoriasis with treatment failure, contraindication or intolerability to at least 1 systemic treatment (including methotrexate, ciclosporin or photo-therapy).

A PASI of ≥ 10 was used as inclusion criterion for the severity grade of the plaque psoriasis. This concurs with the definition of the European regulatory authority's guideline for patients with moderate to severe plaque psoriasis [7]. The European consensus, which also the German guideline refers to, defines moderate to severe psoriasis as a PASI of > 10 or a body surface area (BSA) of > 10 and a DLQI of > 10, however [8] (see Section 2.6.2.4.3 of the full dossier assessment for an explanation of the parameters). The definition of the severity grade used by the company was considered to be sufficient for the present benefit assessment (see Section 2.6.2.4.1 of the full dossier assessment). The results of the patient population with PASI ≥ 10 and DLQI > 10 are presented in Appendix B as additional information.

A total of 302 patients were randomly assigned to treatment with ixekizumab (N = 136) or ustekinumab (N = 166). Randomization of the patients was stratified by the factors body weight (≤ 100 kg versus > 100 kg) and study centre.

Treatment in both study arms was conducted according to the regimen described in Table 7 and was in compliance with the recommendations of the SPCs [9,10].

Primary outcome of the study is the PASI 90 at week 12. Secondary outcomes are remission (PASI 100), outcomes on symptoms and health-related quality of life, and side effects at week 12.

The study is still ongoing, and the present assessment was based on analyses of a planned interim analysis at week 24.

Characteristics of the study 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. ustekinumab

Study Characteristics Category	**Ixekizumab**	**Ustekinumab**
IXORAS	N = 136	N = 166
Age [years], mean (SD)	42.7 (12.7)	44.0 (13.3)
Sex [F/M], %	33.8/66.2	32.5/67.5
Ethnic origin		
Caucasian, n (%)	125 (91.9)	157 (94.6)
Other[a]	11 (8.1)[b]	9 (5.4)[b]
PASI, mean (SD)	19.9 (8.2)	19.8 (9.0)
PASI ≥ 20, n (%)	51 (37.5)	59 (35.5)
Scalp affected, n (%)	120 (88.2)	152 (91.6)
Face and neck affected, n (%)	62 (45.6)	87 (52.4)
Fingernails affected, n (%)	84 (61.8)	105 (63.3)
Genital area affected, n (%)	41 (30.1)	65 (39.2)
BSA [%], mean (SD)	26.7 (16.5)	27.5 (16.7)
DLQI, mean (SD)	11.1 (7.2)	12.0 (7.3)
Patients with DLQI > 10, n (%)	71 (52.2)	85 (51.2)
Time since first diagnosis of psoriasis [years], mean (SD)	17.2 (11.0)	17.8 (12.0)
Number of patients with systemic pretreatment, n (%)		
No prior systemic therapy[c]	9 (6.6)	14 (8.4)
Only nonbiologics	109 (80.1)	127 (76.5)
Only biologics	1 (0.7)	0
Biologics and nonbiologics	17 (12.5)	25 (15.1)
Treatment discontinuation, n (%)	5 (3.7)	8 (4.8)
Study discontinuation, n (%)	2 (1.5)	5 (3.0)

a: The category "other" is composed of patients of African or African American heritage, Asians and patients with several ethnicities or unknown ethnicity.
b: Institute's calculation.
c: Patients with contraindication or intolerance to systemic treatment.
BSA: body surface area; DLQI: Dermatology Life Quality Index; F: female; M: male; n: number of patients in the category; N: number of randomized patients; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Despite a planned 1:1 randomization, there were about 20% more patients in the ustekinumab arm of the IXORAS study than in the ixekizumab arm (see Section 2.6.2.4.1 of the full dossier assessment). Irrespective of this, the patient characteristics between the treatment groups are sufficiently balanced.

The mean age of the patients was between 43 and 44 years. The time point of the first diagnosis of the plaque psoriasis was 17 and 18 years before study inclusion.

Somewhat more than half of the patients had a DLQI > 10. The mean PASI was about 20, with a PASI ≥ 20 in somewhat more than 1 third of the patients. The mean BSA affected by plaque psoriasis in the patients included was about 27%. Most patients – about 90% – had plaque psoriasis of the scalp. Almost every other patient had plaque psoriasis on the face and/or neck, and about 63% of the patients had psoriasis on the nails.

More than 90% of the patients had already received prior systemic therapy for plaque psoriasis. Due to contraindications or intolerance, 8% had not been able to receive prior systemic therapy.

With about 2% and 4%, the number of study and treatment discontinuations until treatment week 24 was low.

Risk of bias

Table 9 shows the risk of bias at study level.

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

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			
Study IXORAS	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at the study level was rated as low for the study included. 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 2.6.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity

- remission measured with the PASI 100
- itching measured with a numeric rating scale (NRS)
- no psoriasis symptoms
  - on the face and neck
  - in the genital area
  - on the fingernails measured with the Nail Psoriasis Severity Index (NAPSI)
- pain of skin recorded with a visual analogue scale (VAS)
- health status, measured with the European Quality of Life-5 Dimensions (EQ-5D) VAS

- Health-related quality of life
  - measured with the DLQI and the
  - SF-36
- Side effects
  - SAEs
  - discontinuation due to AEs
  - infections and infestations (SOC)
  - 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 B) (see Section 2.6.2.4.3 of the full dossier assessment).

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

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

Study	Outcomes													
	All-cause mortality	Remission (PASI 100)[a]	Symptoms (itching NRS)[b]	Symptoms (pain of skin VAS)	Symptoms (face and neck affected)[c]	Symptoms (genital area affected)[c]	Symptoms (fingernails [NAPSI])[c]	Health status (EQ-5D VAS)	Health-related quality of life (SF-36)	Health-related quality of life (DLQI)	SAEs	Discontinuation due to AEs	Infections and infestations (SOC)	General disorders and administration site conditions (SOC)
IXORAS	Yes	Yes	Yes	Yes	No[d]	No[d]	No[d]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: Improvement in PASI score by 100% compared with start of the study.
b: Recorded on a numerical scale (0 to 10).
c: Consideration of the outcome "no psoriasis symptoms" at week 24 in patients with psoriasis on the respective body areas at baseline.
d: No usable data; proportion of patients who were not considered in the analysis was too large (see Section 2.6.2.4.3 of the full dossier assessment).

AE: adverse event; DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life-5 Dimensions; NAPSI: Nail Psoriasis Severity Index; NRS: numeric rating scale; PASI: Psoriasis Area and Severity Index; 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

2.4.2.2 Risk of bias

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

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

Study		Outcomes													
	Study level	All-cause mortality	Remission (PASI 100)[a]	Symptoms (itching NRS)[b]	Symptoms (pain of skin VAS)	Symptoms (face and neck affected)[c]	Symptoms (genital area affected)[c]	Symptoms (fingernails [NAPSI])[c]	Health status (EQ-5D VAS)	Health-related quality of life (SF-36)	Health-related quality of life (DLQI)	SAEs	Discontinuation due to AEs	Infections and infestations (SOC)	General disorders and administration site conditions (SOC)
IXORAS	L	L	L	L	L	-[d]	-[d]	-[d]	L	L	L	L	L	L	L

a: Improvement in PASI score by 100% compared with start of the study.
b: Recorded on a numerical scale (0 to 10).
c: Consideration of the outcome "no psoriasis symptoms" at week 24 in patients with psoriasis on the respective body areas at baseline.
d: No usable data; proportion of patients who were not considered in the analysis was too large (see Section 2.6.2.4.3 of the full dossier assessment).
AE: adverse event; DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life-5 Dimensions; L: low; NAPSI: Nail Psoriasis Severity Index; NRS: numeric rating scale; PASI: Psoriasis Area and Severity Index; 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. This concurs with the company's assessment.

There were no usable data for the outcomes "face and neck affected", "genital area affected" and "fingernails affected".

2.4.2.3 Results

Table 12 and Table 13 summarize the results on the comparison of ixekizumab with ustekinumab in patients with plaque psoriasis. Where necessary, the data from the company's dossier were supplemented with calculations conducted by the Institute.

The Peto odds ratio (Peto OR) offers a good approximation of the relative risk in certain situations (see Section 2.6.2.2 of the full dossier assessment) [11]. Hence in these situations the Peto OR was calculated as estimator for the relative risk and used for the assessment.

The outcomes "PASI 90" and "PASI 75" are presented as additional information in the following Table 12, but were not used for the assessment of the added benefit because of the uncertainty in the interpretation of the results (see Section 2.6.2.4.3 of the full dossier assessment).

The common AEs are presented in Appendix B of the full dossier assessment.

Table 12: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous data) – RCT, direct comparison: ixekizumab vs. ustekinumab

Study Outcome category Outcome	Ixekizumab		Ustekinumab		Ixekizumab vs. ustekinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]; p-value[b]
IXORAS					
Mortality					
All-cause mortality	136	0	166	0	NC
Morbidity					
Remission (PASI 100)[c]	136	67 (49.3)	166	39 (23.5)	2.10 [1.52; 2.90]; < 0.001
Response (PASI 90)[d]	*136*	*113 (83.1)*	*166*	*98 (59.0)*	*1.41 [1.21; 1.63]; < 0.001*
Response (PASI 75)[d]	*136*	*124 (91.2)*	*166*	*136 (81.9)*	*1.11 [1.02; 1.22]; 0.023*
Symptoms					
No psoriasis symptoms					
Face and neck				No usable data[e]	
Genital area				No usable data[e]	
Fingernails[f]				No usable data[e]	
Health-related quality of life					
DLQI (0 or 1)	136	90 (66.2)	166	88 (53.0)	1.25 [1.04; 1.50]; 0.022
Side effects					
AEs (supplementary information)	135	94 (69.6)	166	125 (75.3)	–
SAEs	135	3 (2.2)	166	5 (3.0)	0.74 [0.18; 3.03]; 0.689
Discontinuation due to AEs	135	2 (1.5)	166	1 (0.6)	2.43 [0.25; 23.83][g]; 0.592
Infections and infestations	135	57 (42.2)	166	87 (52.4)	0.81 [0.63; 1.03][h]; 0.081
General disorders and administration site conditions	135	26 (19.3)	166	5 (3.0)	6.39 [2.52; 16.20][h]; 0.001

a: Analyses without model from 2x2 table. Missing data imputed using NRI. Regarding side effect outcomes, the company did not state whether NRI was used.
b: Institute's calculation, unconditional exact test (CSZ method according to [12]).
c: Improvement in PASI score by 100% compared with start of the study.
d: Presented as additional information; outcome is not used for the derivation of the added benefit (see Section 2.6.2.4.3 of the full dossier assessment).
e: Proportion of patients who were not considered in the analysis is too large.
f: Recorded using NAPSI; no psoriasis symptoms when NAPSI score of 0 is reached.
g: Peto OR as estimate for the relative risk; Institute's calculation, see Section 2.6.2.2 of the full dossier assessment.
h: Institute's calculation of RR and CI (asymptotic).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; DLQI: Dermatology Life Quality Index; n: number of patients with (at least 1) event; N: number of analysed patients; NAPSI: Nail Psoriasis Severity Index; NC: not calculated; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

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

Study Outcome category Outcome	Ixekizumab			Ustekinumab			Ixekizumab vs. ustekinumab
	N[a]	Values at start of study mean (SD)	Change at week 24 mean[b] (SE)	N[a]	Values at start of study mean (SD)	Change at week 24 mean[b] (SE)	MD [95% CI]; p-value[b]
IXORAS							
Morbidity							
Symptoms							
Itching NRS	134	6.3 (2.7)	1.3 (0.2)	165	6.2 (2.6)	1.7 (0.2)	−0.39 [−0.83; 0.04]; 0.075
Pain of skin VAS	134	42.9 (33.3)	−35.7 (1.3)	165	39.4 (30.8)	−32.8 (1.2)	−2.87 [−5.96; 0.21]; 0.068
Health status							
EQ-5D VAS	133	66.3 (22.2)	15.3 (1.7)	163	67.4 (22.4)	10.8 (1.6)	4.56 [0.45; 8.66]; 0.030 Hedges' g: 0.25 [0.02; 0.48][c]
Health-related quality of life							
SF-36 sum score							
PCS	132	47.3 (9.5)	5.5 (0.6)	163	48.4 (9.8)	3.5 (0.5)	1.93 [0.49; 3.37]; 0.009 Hedges' g: 0.31 [0.08; 0.54][c]
MCS	132	47.1 (11.5)	3.8 (0.8)	163	46.5 (11.9)	3.1 (0.8)	0.71 [−1.32; 2.75]; 0.491

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: MMRM analysis for change of end of the study compared with start of the study without imputation of missing data.
c: Institute's calculation, see Section 2.6.2.2 of the full dossier assessment.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; MCS: Mental Component Summary; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of patients with baseline and at least 1 subsequent value; NRS: numeric rating scale; 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; vs.: versus

Based on the available data, at most indications, e.g. of an added benefit, can be determined for the outcomes presented in Table 12 and Table 13.

Mortality

All-cause mortality

No deaths occurred in the IXORAS study up to treatment week 24. There was no hint of an added benefit of ixekizumab in comparison with ustekinumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Remission (PASI 100)

A statistically significant difference in favour of ixekizumab was shown for the outcome "remission" (measured with the PASI 100). There was an indication of an added benefit of ixekizumab in comparison with ustekinumab.

This concurs with the company's assessment.

Symptoms: itching

For the symptom outcome "itching", the mean change in itching on a numerical scale from baseline to treatment week 24 was considered. There was no statistically significant difference between the treatment groups for this outcome. Hence there was no hint of an added benefit of ixekizumab in comparison with ustekinumab; an added benefit is therefore not proven.

The company considered responder analyses of a subpopulation for this outcome and derived an indication of an added benefit from this.

Symptoms: pain of skin (VAS)

There was no statistically significant difference between the treatment groups for the symptom outcome "pain of skin" (recorded with a VAS). Hence there was no hint of an added benefit of ixekizumab in comparison with ustekinumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Symptoms: no psoriasis symptoms face/neck, genital area or fingernails

There were no usable data for the symptom outcome "no psoriasis symptoms on face/neck, in the genital area or on the fingernails (recorded using the NAPSI)". In each case, the company used the subpopulation of patients with psoriasis on the respective body areas at baseline for its analyses. These analyses did not consider an important proportion of the randomized patients and were therefore unsuitable for the derivation of the added benefit (see Section 2.6.2.4.3 of the full dossier assessment). There was no hint of an added benefit of ixekizumab in comparison with ustekinumab for any these outcomes; an added benefit is therefore not proven.

For the outcome “no psoriasis symptoms on the face/neck or in the genital area”, this concurs with the assessment of the company. For the outcome “no psoriasis symptoms on the fingernails” (recorded with the NAPSI), the company derived an indication of an added benefit.

Health status

A statistically significant difference in favour of ixekizumab in comparison with ustekinumab was shown for the outcome “health status” measured with the EQ-5D VAS. However, the 95% confidence interval (CI) of the standardized mean difference (Hedges’ g) was not fully outside the irrelevance range of −0.2 to 0.2 so that the effect was not to be rated as relevant. Hence there was no hint of an added benefit of ixekizumab in comparison with ustekinumab for the outcome “health status”; an added benefit is therefore not proven.

This concurs with the company’s assessment.

Health-related quality of life

SF-36 − Physical Component Summary

A statistically significant difference in favour of ixekizumab in comparison with ustekinumab was shown for the Physical Component Summary (PCS) of the SF-36. However, the 95% CI of the standardized mean difference (Hedges’ g) was not fully outside the irrelevance range of −0.2 to 0.2 so that the effect was not to be rated as relevant. Hence there was no hint of an added benefit of ixekizumab in comparison with ustekinumab for the outcome “PCS”; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an indication of an added benefit on the basis of a responder analysis.

SF-36 − Mental Component Summary

No statistically significant difference between the treatment groups was shown for the Mental Component Summary (MCS) of the SF-36. Hence there was no hint of an added benefit of ixekizumab in comparison with ustekinumab; an added benefit is therefore not proven.

This concurs with the company’s assessment.

DLQI (0 or 1)

Regarding the proportion of patients who achieved a DLQI score of 0 or 1 at week 24, there was a statistically significant difference in favour of ixekizumab in comparison with ustekinumab. This resulted in an indication of an added benefit of ixekizumab in comparison with ustekinumab.

This concurs with the company’s assessment.

Side effects

Serious adverse events, discontinuation due to adverse events as well as infections and infestations

No statistically significant difference between the treatment groups was shown for any of the outcomes "SAEs", "discontinuation due to AEs" and "infections and infestations". Hence there was no hint of greater or lesser harm of ixekizumab in comparison with ustekinumab for these outcomes. Greater or lesser harm is therefore not proven for these outcomes.

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 outcome "general disorders and administration site conditions". This resulted in an indication of greater harm from ixekizumab in comparison with ustekinumab.

This concurs with the assessment of the company, which, on the basis of the analysis on the outcome "injection site reactions", arrived at the same conclusion.

2.4.2.4 Subgroups and other effect modifiers

The following effect modifiers were considered in the benefit assessment:

- sex (female/male)
- age (< 65 years/≥ 65 years)
- region (Western Europe/Eastern Europe/North America)
- disease severity (PASI < 20/PASI ≥ 20)

Only the results with at least an indication of an interaction between treatment and subgroup characteristic are presented. The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least 1 subgroup.

Table 14 shows the results of the subgroup analysis.

Table 14: Subgroups (health-related quality of life) – RCT, direct comparison: ixekizumab vs. ustekinumab

Study Outcome Characteristic Subgroup	Ixekizumab N	Ixekizumab Patients with event n (%)	Ustekinumab N	Ustekinumab Patients with event n (%)	Ixekizumab vs. ustekinumab RR [95% CI][a]	Ixekizumab vs. ustekinumab p-value[a]
IXORAS						
DLQI (0 or 1)						
Sex						
Women	46	26 (56.52)	54	30 (55.56)	1.02 [0.72; 1.44][b]	0.923[b]
Men	90	64 (71.11)	112	58 (51.79)	1.37 [1.10; 1.71][b]	0.005[b]
Total					Interaction:	0.155[c]
Age						
< 65 years	123	84 (68.29)	151	86 (56.95)	1.20 [1.0; 1.44]	0.053
≥ 65 years	6	6 (100)	9	2 (22.22)	3.71 [1.25; 11.08]	0.019
Total					Interaction:	0.046[c]

a: Institute's calculation; meta-analysis with random effects.
b: Missing data were imputed using NRI.
c: p-value from Q test for heterogeneity.
CI: confidence interval; DLQI: Dermatology Life Quality Index; G-BA: Federal Joint Committee; n: number of patients with (at least 1) event; N: number of analysed patients; NRI: non-responder imputation; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Health-related quality of life

DLQI (0 or 1)

For the outcome "DLQI (0 or 1)", there was an indication of an effect modification by the characteristic "sex" and proof of an effect modification by the characteristic "age". The subgroup results could not be meaningfully interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing. The derivation of the added benefit was therefore conducted on the basis of the results on the total population.

This concurs with the company's assessment.

2.4.3 Probability and extent of added benefit

The derivation of probability and extent of 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

Based on the data presented in Section 2.4.2, there was an indication of an added benefit for the outcomes “remission” (recorded using the PASI 100) and “disease-specific health-related quality of life” (recorded using the DLQI [0 or 1]) for patients with plaque psoriasis with inadequate response to other systemic treatments or who are unsuitable for these treatments. There was an indication of greater harm for the specific AE “general disorders and administration site conditions”.

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: ixekizumab vs. ustekinumab

Outcome category **Outcome** **Effect modifier**	**Ixekizumab vs. ustekinumab** **Proportion of events or mean change** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
Remission (PASI 100)	49.3% vs. 23.5% RR: 2.10 [1.52; 2.90] RR: 0.48 [0.34; 0.66][c] p < 0.001 probability: "indication"	Outcome category "non-serious/non-severe symptoms/late complications" $CI_u \leq 0.80$ added benefit, extent: "considerable"
NRS itching	1.3 vs. 1.7 MD: −0.39 [−0.83; 0.04]; p = 0.075	Lesser benefit/added benefit not proven
Pain of skin VAS	−35.7 vs. −32.8 MD: −2.87 [−5.96; 0.21] p = 0.068	Lesser benefit/added benefit not proven
No psoriasis symptoms		
Face and neck	No usable data	Lesser benefit/added benefit not proven
Genital area	No usable data	Lesser benefit/added benefit not proven
Fingernails	No usable data	Lesser benefit/added benefit not proven
Health status EQ-5D VAS	15.3 vs. 10.8 MD: 4.56 [0.45; 8.66]; p = 0.030 Hedges' g: 0.25 [0.02; 0.48]	Lesser benefit/added benefit not proven[d]
Health-related quality of life		
SF-36 sum score		
PCS	5.5 vs. 3.5 MD: 1.93 [0.49; 3.37]; p = 0.009 Hedges' g: 0.31 [0.08; 0.54]	Lesser benefit/added benefit not proven[d]
MCS	3.8 vs. 3.1 MD: 0.71 [−1.32; 2.75] p = 0.491	Lesser benefit/added benefit not proven
DLQI (0 or 1)	66.2% vs. 53.0% RR: 1.25 [1.04; 1.50] RR: 0.80 [0.67; 0.96][c] p = 0.022 probability: "indication"	Outcome category "health-related quality of life" $0.90 < CI_u \leq 1.00$ added benefit, extent: "minor"

(continued)

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

Outcome category **Outcome** **Effect modifier**	**Ixekizumab vs. ustekinumab** **Proportion of events or mean change** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	2.2% vs. 3.0% RR: 0.74 [0.18; 3.03] p = 0.689	Greater/lesser harm not proven
Discontinuation due to AEs	1.5% vs. 0.6% POR: 2.43 [0.25; 23.83] p = 0.592	Greater/lesser harm not proven
Infections and infestations	42.2% vs. 52.4% RR: 0.81 [0.63; 1.03] p = 0.081	Greater/lesser harm not proven
General disorders and administration site conditions	19.3% vs. 3.0% RR: 6.39 [2.52; 16.20]; RR: 0.16 [0.06; 0.40][c] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u \leq 0.80$ greater harm, extent: "considerable"

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: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d: If the CI of the standardized mean difference (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.
AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life-5 Dimensions; MCS: Mental Component Summary; NRS: numeric rating scale; PASI: Psoriasis Area and Severity Index; PCS: Physical Component Summary; POR: Peto odds ratio; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; VAS: visual analogue scale; vs.: versus

2.4.3.2 Overall conclusion on added benefit

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 ixekizumab in comparison with ustekinumab

Positive effects	**Negative effects**
Outcome category: non-serious/non-severe symptoms/late complications: ▪ remission (PASI 100): indication of an added benefit – extent: "considerable"	Outcome category: non-serious/non-severe side effects: ▪ general disorders and administration site conditions: indication of greater harm – extent: "considerable"
Outcome category: health-related quality of life: ▪ DLQI (0 or 1): indication of an added benefit – extent: "minor"	
DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index	

In the overall consideration, there are positive effects of ixekizumab in the outcome categories "morbidity" and "health-related quality of life" and a negative effect in the outcome category "side effects".

On the side of positive effects, there was an indication of considerable added benefit in comparison with the ACT for the outcome "PASI 100". For the outcome category "health-related quality of life", there was an indication of a minor added benefit of ixekizumab in comparison with ustekinumab for the outcome "DLQI (0 or 1)".

The positive effects are in contrast to a negative effect in the category of non-serious/non-severe side effects. There was an indication of greater harm with the extent "considerable" for the outcome "general disorders and administration site conditions". This did not challenge the positive effects of ixekizumab.

In summary, there is an indication of considerable added benefit of ixekizumab in comparison with ustekinumab for adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or PUVA, or with contraindication or intolerance to such treatments.

2.4.4 List of included studies

IXORAS-Studie (RHBS)

Eli Lilly and Company. A 52-week multicenter, randomized, blinded, parallel-group study comparing the efficacy and safety of ixekizumab to ustekinumab in patients with moderate-to-severe plaque psoriasis: study I1F-MC-RHBS; 24-week clinical study report [unpublished]. 2016.

Eli Lilly and Company. A study of ixekizumab (LY2439821) in participants with moderate-to-severe plaque psoriasis (IXORA-S): full text view [online]. In: ClinicalTrials.gov. 30.01.2017 [Accessed: 13.03.2017]. URL: https://clinicaltrials.gov/show/NCT02561806.

Eli Lilly and Company. A 52-week multicenter, randomized, blinded, parallel group study comparing the efficacy and safety of ixekizumab to ustekinumab in patients with moderate to severe plaque psoriasis: protocol I1F-MC-RHBS [online]. In: EU Clinical Trials Register. [Accessed: 13.03.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-000892-28.

Eli Lilly and Company. A 52-week multicenter, randomized, blinded, parallel-group study comparing the efficacy and safety of ixekizumab to ustekinumab in patients with moderate-to-severe plaque psoriasis: study I1F-MC-RHBS(a); clinical protocol [unpublished]. 2016.

2.5 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**[a]	**ACT**[b]	**Probability and extent of added benefit**
A	Adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy[c]	**Fumaric acid esters** or ciclosporin or **methotrexate** or phototherapy (balneo-phototherapy, oral PUVA, NB-UVB)**d**	Added benefit not proven
B	Adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or PUVA, or with contraindication or intolerance to such treatments	Adalimumab or infliximab or **ustekinumab**[d]	Indication of considerable added benefit

a: It is a precondition that only patients are treated for whom topical treatment alone is inadequate.
b: 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.
c: This population includes all patients in the approved therapeutic indication less the patients named in research question B.
d: Dosage of the ACT was to concur with the recommendations of the relevant SPCs. A dose-fair comparison under exhaustion of the approval-compliant dosage (if tolerated) was to be conducted.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); PUVA: psoralen and ultraviolet-A light; SPC: Summary of Product Characteristics

In summary, the added benefit of ixekizumab is not proven for patients with plaque psoriasis who are candidates for systemic therapy (research question A). There is an indication of considerable added benefit of ixekizumab in comparison with ustekinumab for patients with plaque psoriasis with inadequate response to other systemic treatments or who are unsuitable for these treatments (research question B).

This assessment deviates from that of the company. The company claimed an indication of major added benefit of ixekizumab both for patients who are candidates for systemic therapy (research question A) and for patients with plaque psoriasis with inadequate response to other systemic treatments or who are unsuitable for these treatments (research question B).

The approach for deriving an overall conclusion on 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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