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Ixekizumab (plaque psoriasis) –

Addendum to Commission A17-07[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
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
NAPPA-Clin	Nail Assessment in Psoriasis and Psoriatic Arthritis – Clinical Assessment of Severity
NAPSI	Nail Psoriasis Severity Index
NRS	numeric rating scale
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PUVA	psoralen and ultraviolet-A light
RCT	randomized controlled trial
SAE	serious adverse event
SOC	System Organ Class
SF-36	Short Form (36) Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
UVB	ultraviolet-B light
VAS	visual analogue scale

1 Background

On 11 July 2017, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-07 (Ixekizumab – Benefit assessment according to §35a Social Code Book V [1]).

In Module 4 A [2] of its dossier on ixekizumab, the pharmaceutical company (hereinafter referred to as "the company") presented the study RHBZ for the therapeutic indication of plaque psoriasis in patients who are candidates for systemic therapy. The study was not included in the assessment because the proportion of patients who had already been pretreated with phototherapy was too large. Detailed reasons can be found in dossier assessment A17-07 [1]. With its written comments [3,4] and after the oral hearing [5], the company submitted supplementary analyses of the RHBZ study.

The G-BA commissioned IQWIG with the assessment of the RHBZ study under consideration of the information provided in the dossier and the analyses submitted by the company in the commenting procedure. The commission additionally comprised the assessment of the outcome "Nail Psoriasis Severity Index (NAPSI)" from the IXORAS study, which was also presented in the dossier.

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

2 Assessment

2.1 Assessment of study RHBZ (research question A)

2.1.1 Research question and study characteristics

Research question A of the benefit assessment of ixekizumab was the assessment of the added benefit in patients with moderate to severe plaque psoriasis who are candidates for systemic and/or phototherapy. For this research question, the company had presented the RHBZ study in its dossier.

Study RHBZ was a randomized controlled trial (RCT) in patients with moderate to severe plaque psoriasis. The patients had not received prior systemic treatment; about 40% of the patients had received phototherapy before inclusion into the study, however. The phototherapy consisted of treatment with psoralen and ultraviolet-A light (PUVA) in 14% of the patients, and of treatment with ultraviolet-B light (UVB) in 22% of the patients. It was unclear for 6% of the patients which form of phototherapy they had received. Study RHBZ was not used for dossier assessment A17-07 because of this large proportion of patients who had already received phototherapy.

The discussion in the oral hearing [6] showed that pretreatment with UVB is not considered to be a systemic treatment. With its comments [3,4], the company presented new analyses of the RHBZ study, which did not include the data of the patients pretreated with PUVA or unclear phototherapy. The present assessment was based on these analyses. After the oral hearing, the company again submitted further analyses of the RHBZ study [5]. These analyses were based on the total patient population, however, and were not used for the assessment.

The RHBZ 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. The study design and the interventions of the RHBZ study were already presented in the dossier assessment of ixekizumab [1].

The following Table 1 shows the characteristics of the patients in the study included.

Table 1: Characteristics of the study population – RCT, direct comparison: ixekizumab vs. fumaric acid esters vs. methotrexate (subpopulation without pretreatment with PUVA or unclear phototherapy)

Study **Characteristics** **Category**	**Ixekizumab**	**Fumaric acid esters**	**Methotrexate**
RHBZ	N = 40[a]	N = 43[a]	N = 48[a]
Age [years], mean (SD)	44 (14)	42 (14)	38 (12)
Sex [F/M], %	28/73	23/77	35/65
BMI [kg/m^2] mean (SD)	30.1 (6.4)	29.6 (7.4)	27.8 (5.4)
Ethnic origin			
Caucasian, n (%)	33 (82.5)	34 (79.1)	37 (77.1)
Other[b], n (%)	7 (17.5)	9 (20.9)	11 (22.9)
PASI, mean (SD)	19.5 (8.7)	19.7 (8.8)	17.7 (7.3)
PASI ≥ 20, n (%)	17 (42.5)	20 (46.5)	16 (33.3)
Scalp involvement, n (%)	34 (85.0)	37 (86.0)	40 (83.3)
Face and neck involvement, n (%)	27 (67.5)	27 (62.8)	32 (66.7)
Fingernail and toenail involvement, n (%)	23 (57.5)	21 (48.8)	22 (45.8)
Genital involvement, n (%)	14 (35.0)	21 (48.8)	22 (45.8)
BSA, mean (SD)	26.4 (17.2)	24.5 (17.0)	24.3 (15.2)
DLQI, mean (SD)	14.6 (5.2)	17.2 (6.3)	16.7 (5.3)
Patients with DLQI > 10, n (%)	35 (87.5)	38 (88.4)	45 (93.8)
Time since first diagnosis of psoriasis [years], mean (SD)	13.7 (14.0)	13.5 (13.6)	12.4 (10.5)
Treatment discontinuation, n (%)	ND	ND	ND
Study discontinuation, n (%)	3 (7.5)	23 (53.5)	2 (4.2)

a: Without those patients who were pretreated with PUVA or unknown phototherapy (total population: ixekizumab N = 54, fumaric acid esters N = 54; methotrexate N = 54).
b: The category "Other" includes Asians and patients with several ethnicities.
BMI: body mass index; BSA: body surface area in %; DLQI: Dermatology Life Quality Index; F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; PASI: Psoriasis Area and Severity Index; PUVA: psoralen and ultraviolet-A light; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Patient characteristics were largely balanced between the 3 treatment arms. The mean age of the patients was about 40 years; most of them were male and Caucasian. The average Psoriasis Area and Severity Index (PASI) at the start of the study was just below 20. During the study, more than half of the patients in the fumaric acid ester arm discontinued the study. This was mostly due to adverse events (AEs).

Table 2 shows the risk of bias at study level.

Table 2: Risk of bias at study level – RCT, direct comparison: ixekizumab vs. fumaric acid esters

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			
RHBZ	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

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

The lack of blinding of patients and treating staff influenced the assessment of the risk of bias at outcome level.

2.1.2 Results on added benefit

The assessment of the added benefit was based on the comparison of the ixekizumab arm with the fumaric acid ester arm of the RHBZ study.

The results on AEs, except for the outcome “discontinuation due to AEs”, could not be used for the assessment because of the high rate of discontinuation in the fumaric acid ester arm and the unclear treatment and observation duration in this study arm.

In addition, the methotrexate arm of the study could not be used for the following reason: According to the Summary of Product Characteristics (SPC) [7], methotrexate is only approved for the most severe forms of plaque psoriasis. The company did not show that methotrexate was the adequate treatment for all patients in the sense of the approval.

The assessment for the comparison of ixekizumab versus fumaric acid esters was based on analyses that excluded the data of the patients pretreated with PUVA or unclear phototherapy. Tables with the common AEs in this population can be found in Appendix A.

Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - remission measured with the PASI 100
  - itching measured with a numeric rating scale (NRS)
  - pain of skin (visual analogue scale [VAS])
  - no psoriasis symptoms
    - on the face and neck
    - in the genital area
  - nail involvement measured with the Nail Assessment in Psoriasis and Psoriatic Arthritis – Clinical Assessment of Severity (NAPPA-Clin)
  - health status, measured with the European Quality of Life-5 Dimensions (EQ-5D) VAS
- Health-related quality of life
  - measured with the Dermatology Life Quality Index (DLQI) and the
  - Short Form (36) Health Survey (SF-36)
- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to AEs
  - infections and infestations (System Organ Class [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 A).

Table 3 shows for which outcomes data were available in the studies included.

Table 3: Matrix of outcomes – RCT, direct comparison: ixekizumab vs. fumaric acid esters

Study	Outcomes												
	All-cause mortality	Remission (PASI 100)[a]	Symptoms (itching NRS)[b]	Symptoms (pain of skin VAS)	Symptoms (face and neck involvement)[c]	Symptoms (genital involvement)	Symptoms (nail involvement [NAPPA-Clin])	Health status (EQ-5D VAS)	Health-related quality of life (SF-36)	Health-related quality of life (DLQI)	SAEs	Discontinuation due to AEs	Specific AEs[c]
RHBZ	Y	Y	Y	Y	Y	Y	No	Y	No	Y	No	Y	No

a: Improvement in PASI score by 100% compared with start of the study.
b: Recorded on a numerical scale (0 to 10).
c: The following events (MedDRA coding) are considered: infections and infestations (SOC).
AE: adverse event; DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; NAPPA-Clin: Nail Assessment in Psoriasis and Psoriatic Arthritis – Clinical Assessment of Severity; 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; Y: yes

Risk of bias

Table 4 describes the risk of bias at outcome level.

Table 4: Risk of bias at study and outcome level – RCT, direct comparison: ixekizumab vs. fumaric acid esters

Study		Outcomes												
	Study level	All-cause mortality	Remission (PASI 100)[a]	Symptoms (itching NRS)[b]	Symptoms (pain of skin VAS)	Symptoms (face and neck involvement)[c]	Symptoms (genital involvement)	Symptoms (nail involvement [NAPPA-Clin])	Health status (EQ-5D VAS)	Health-related quality of life (SF-36)	Health-related quality of life (DLQI)	SAEs	Discontinuation due to AEs	Specific AEs
RHBZ	L	–	H	H	H	H	H	–	H	–	H	–	H	–

a: Improvement in PASI score by 100% compared with start of the study.
b: Recorded on a numerical scale (0 to 10).
c: The following events (MedDRA coding) are considered: infections and infestations (SOC).
–: No usable data or no analysis conducted because no events occurred.
AE: adverse event; DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; NAPPA-Clin: Nail Assessment in Psoriasis and Psoriatic Arthritis – Clinical Assessment of Severity; 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 high for all outcomes for which usable data were available.

This was mainly caused by the potentially informative censoring because of the discontinuations due to AEs in the fumaric acid ester arm of the study. In relation to the relevant patient population, which was not pretreated with PUVA or unknown phototherapy, 23 (53%) patients discontinued the study prematurely in the fumaric acid ester arm, 16 (37%) of which discontinued due to AEs. In contrast, this only applied to 3 (8%) patients in the ixekizumab arm, 1 (3%) of which due to AEs. It is unclear when the study discontinuations associated with AEs occurred and to what extent treatment and observation durations differed between the study arms.

For the patient-reported outcomes (itching, pain of skin VAS, European Quality of Life-5 Dimensions VAS, and DLQI) and for the outcome “discontinuation due to AEs”, the high risk of bias was also caused by the lack of blinding.

Results

Table 5 and Table 6 summarize the results on the comparison of ixekizumab with fumaric acid esters in patients with plaque psoriasis.

Table 5: Results (mortality, morbidity, health-related quality of life and side effects, event time analysis) – RCT, direct comparison: ixekizumab vs. fumaric acid esters (subpopulation without pretreatment with PUVA or unclear phototherapy)

Study **Outcome category**	**Ixekizumab**		**Fumaric acid esters**		**Ixekizumab vs. fumaric acid esters**
Outcome	**N**	**Median survival time in days [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in days [95% CI]** **Patients with event n (%)**	**HR [95% CI][a]; p-value**
RHBZ					
Mortality					
All-cause mortality	40	NA 0 (0)	41	NA 0 (0)	ND
Morbidity					
Remission (PASI 100)	40	143.0 [85.0; 183.0] 24 (60.0)	43	NA 1 (2.3)	18.40 [2.49; 136.19]; 0.004
Response (PASI 90)	*40*	*58.0 [57.0; 85.0]* *36 (90.0)*	*43*	*NA* *3 (7.0)*	*21.72 [6.54; 72.14]; < 0.001*
Response (PASI 75)	*40*	*29.5 [29.0; 57.0]* *38 (95.0)*	*43*	*142.0 [113.0; NA]* *11 (25.6)*	*20.80 [8.16; 53.07]; < 0.001*
Symptoms					
No psoriasis symptoms					
Face and neck	40	59.5 [30.0; 109.0] 27 (67.5)	43	NA [120.0; NA] 9 (20.9)	3.00 [1.41; 6.38]; 0.004
Genital area	40	NA [119.0; NA] 13 (32.5)	43	NA [97.0; NA] 7 (16.3)	1.53 [0.61; 3.86]; 0.369
Nail involvement (NAPPA-Clin score)				No usable data	
Itching NRS[b]	40	28 [15.0; 57.0] 31 (77.5)	43	92.0 [83.0; 120.0] 20 (46.5)	1.96 [1.11; 3.47]; 0.020
Health-related quality of life					
DLQI (0 or 1)	40	86.0 [59.0; 113.0] 27 (67.5)	43	173.0 [120.0; NA] 9 (20.9)	2.77 [1.30; 5.92]; 0.008
Side effects					
AEs (supplementary information)	40	ND 34 (85.0)	41	ND 37 (90.2)	–
SAEs				No usable data	
Discontinuation due to AEs	40	ND 1 (2.5)	41	ND 16 (39.0)	RR: 0.06 [0.01; 0.46]; < 0.001
Infections and infestations				No usable data	

a: Unless stated otherwise.
b: Time to a reduction in itching by ≥ 4 points of a 0–10 scale.
AE: adverse event; CI: confidence interval; DLQI: Dermatology Life Quality Index; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NAPPA-Clin: Nail Assessment in Psoriasis and Psoriatic Arthritis – Clinical Assessment of Severity; ND: no data; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 6: Results (morbidity and health-related quality of life, continuous) – ixekizumab vs. fumaric acid esters (subpopulation without pretreatment with PUVA or unclear phototherapy)

Study Outcome category	Ixekizumab			Fumaric acid esters			Ixekizumab vs. fumaric acid esters
Outcome	**N**	**Values at start of study mean (SD)**	**Values at end of study mean[a] (SE)**	**N**	**Values at start of study mean (SD)**	**Values at end of study mean[a] (SE)**	**MD [95% CI]; p-value**
RHBZ							
Morbidity							
Pain of skin VAS[c]	ND[b]	41.1 (27.2)	8.1 (2.8)	ND[b]	43.1 (30.8)	24.5 (3.8)	−16.35 [−25.72;−6.98]; < 0.001 Hedges' g: −0.96 [−1.55; −0.38]
Health status (EQ-5D VAS)[d]	ND[b]	64.7 (20.2)	84.2 (2.6)	ND[b]	64.7 (26.1)	80.5 (3.6)	3.70 [−5.10; 12.50]; 0.407
Health-related quality of life							
SF-36 PCS	No usable data						
SF-36 MCS	No usable data						

a: LS mean from MMRM number of patients.
b: number of patients unclear; a proportion of more than 70% is assumed.
c: Lower values indicate less pain.
d: Higher values indicate better health status.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; LS: least-square; MCS: Mental Component Summary; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; 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

The risk of bias for all outcomes was assessed as high. Because of this and due to the presence of only one study, at most hints, e.g. of an added benefit, can initially be derived for all outcomes. Due to the very large effects in the outcomes "remission" (PASI 100) and "discontinuation due to AEs", hereinafter indications are derived for these outcomes.

Mortality

All-cause mortality

No deaths occurred in the RHBZ study up to treatment week 24. There was no hint of an added benefit of ixekizumab in comparison with fumaric acid esters; 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 outcome-specific high risk of bias for this outcome. Considering the size of the observed effect, however, it was not assumed that the effect and the extent of the effect were caused by bias alone. There was an indication of an added benefit of ixekizumab in comparison with fumaric acid esters.

Symptoms: itching

A statistically significant difference in favour of ixekizumab, which was no more than marginal, was shown for the outcome "itching". There was no hint of an added benefit of ixekizumab in comparison with fumaric acid esters; an added benefit is therefore not proven.

Symptoms: pain of skin

A statistically significant difference in favour of ixekizumab was shown for the outcome "pain of skin". The 95% confidence interval (CI) of the standardized mean difference (Hedges' g) was fully outside the irrelevance range of −0.2 to 0.2 so that the effect was rated as relevant. There was a hint of an added benefit of ixekizumab in comparison with fumaric acid esters.

Symptoms: no psoriasis symptoms on face/neck

A statistically significant difference in favour of ixekizumab was shown for the outcome "no psoriasis symptoms on face/neck". There was a hint of an added benefit of ixekizumab in comparison with fumaric acid esters.

Symptoms: no psoriasis symptoms in the genital area

There was no statistically significant difference between the treatment groups for the outcome "no psoriasis symptoms in the genital area". Hence there was no hint of an added benefit of ixekizumab in comparison with fumaric acid esters; an added benefit is therefore not proven.

Symptoms: nail involvement (recorded with the NAPPA-Clin)

There were no usable data for the outcome "nail involvement" recorded with the NAPPA-Clin. There was no hint of an added benefit of ixekizumab in comparison with fumaric acid esters; an added benefit is therefore not proven.

Health status

There was no statistically significant difference between the treatment groups for the outcome "health status" measured with the EQ-5D VAS. Hence there was no hint of an added benefit of ixekizumab in comparison with fumaric acid esters; an added benefit is therefore not proven.

Health-related quality of life

SF-36 (MCS and PCS)

There were no usable data for the outcome SF-36 (Mental Component Summary [MCS] and Physical Component Summary [PCS]). There was no hint of an added benefit of ixekizumab in comparison with fumaric acid esters; an added benefit is therefore not proven.

DLQI (0 or 1)

A statistically significant difference in favour of ixekizumab was shown for the outcome "DLQI (0 or 1)". There was a hint of an added benefit of ixekizumab in comparison with fumaric acid esters.

Side effects

Serious adverse events

There were no usable data for the outcome "SAEs". There was no hint of an added benefit of ixekizumab in comparison with fumaric acid esters; an added benefit is therefore not proven.

Discontinuation due to adverse events

A statistically significant difference in favour of ixekizumab was shown for the outcome "discontinuation due to AEs". There was an outcome-specific high risk of bias for this outcome. Considering the size of the observed effect, however, it was not assumed that the effect and the extent of the effect were caused by bias alone. There was an indication of an added benefit of ixekizumab in comparison with fumaric acid esters.

Specific adverse events

There were no usable data for the outcome "specific AEs". There was no hint of an added benefit of ixekizumab in comparison with fumaric acid esters; an added benefit is therefore not proven.

2.1.3 Probability and extent of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level. The different outcome categories and the effect sizes are taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [8].

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.

Assessment of added benefit at outcome level

The data presented in Table 5 and Table 6 resulted in the following assessment of ixekizumab in comparison with fumaric acid esters:

- an indication of an added benefit for the outcome “remission” (PASI 100)
- a hint of an added benefit for each of the following outcomes: itching (NRS), pain of skin (VAS), no psoriasis symptoms on face/neck, and DLQI (0 or 1)
- an indication of lesser harm for the outcome “discontinuation due to AEs”

The extent of the respective added benefit at outcome level was estimated from these results (see Table 7).

Table 7: Extent of added benefit at outcome level: ixekizumab vs. fumaric acid esters

Outcome category **Outcome**	**Ixekizumab vs. fumaric acid esters** **Median of time to event in days, proportion of events or mean at the end of the study** **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)	143.0 vs. NA 60% vs. 2.3% HR: 18.40 [2.49; 136.19] HR: 0.05 [0.01; 0.40][c] p = 0.004 probability: “indication”[d]	Outcome category: non-serious/non-severe symptoms/late complications $CI_u \leq 0.80$ added benefit, extent "considerable"
Itching NRS	28.0 vs. 92.0 77.5% vs. 46.5% HR: 1.96 [1.11; 3.47] HR: 0.51 [0.29; 0.9009][c] p = 0.002 probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[e]
Pain of skin VAS	8.1 vs. 24.5 MD: −16.35 [−25.72; −6.98] p < 0.001 Hedges’ g: −0.96 [−1.55; −0.38][f] probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: “non-quantifiable”
No psoriasis symptoms		
Face and neck	59.5 vs. NA HR: 3.00 [1.41; 6.38] HR: 0.33 [0.16; 0.71][c] p = 0.004 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u \leq 0.80$ added benefit, extent "considerable"
Genital area	NA vs. NA HR: 1.53 [0.61; 3.86] p = 0.369	Lesser benefit/added benefit not proven
Nail involvement	No usable data	

(continued)

Table 7: Extent of added benefit at outcome level: ixekizumab vs. fumaric acid esters (continued)

Outcome category **Outcome**	**Ixekizumab vs. fumaric acid esters** **Median of time to event in days, proportion of events or mean at the end of the study** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Morbidity		
Health status EQ-5D VAS	84.2 vs. 80.5 MD: 3.70 [−5.10; 12.50] p = 0.407	Lesser benefit/added benefit not proven
Health-related quality of life		
DLQI (0 or 1)	86.0 vs. 173.0 HR: 2.77 [1.30; 5.92] HR: 0.36 [0.17; 0.77][c] p = 0.008 probability: “hint”	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.9$ added benefit, extent: “considerable”
SF-36 sum score		
PCS	No usable data	
MCS	No usable data	
Side effects		
SAEs	No usable data	
Discontinuation due to AEs	2.5% vs. 39% RR: 0.06 [0.01; 0.46] p < 0.001 probability: “indication”	Outcome category: non-serious/non-severe side effects $CI_u \leq 0.80$ lesser harm, extent: “considerable”
Specific AEs	No usable data	

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: The certainty of results is considered high because it cannot be assumed that the observation of such a large effect (also in its extent) is explicable solely by the aspects of bias.
e: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
f: If the CI of Hedges’ g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, it cannot be derived that a relevant effect is present.

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; NA: not achieved; NRS: numeric rating scale; PASI: Psoriasis Area and Severity Index; PCS: Physical Component Summary; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; VAS: visual analogue scale; vs.: versus

Overall conclusion on added benefit

Table 8 summarizes the results that were included in the overall conclusion on added benefit.

Table 8: Positive and negative effects from the assessment of ixekizumab in comparison with fumaric acid esters

Positive effects	**Negative effects**
Outcome category: non-serious/non-severe symptoms/late complications: ▪ remission (PASI 100): indication of an added benefit – extent: "considerable" ▪ pain of skin VAS: hint of an added benefit – extent: "non-quantifiable" ▪ no psoriasis symptoms – face and neck: hint of an added benefit – extent: "considerable"	–
Outcome category: health-related quality of life: ▪ DLQI (0 or 1): hint of an added benefit – extent: "considerable"	–
Outcome category: non-serious/non-severe side effects: ▪ discontinuation due to AEs – indication of an added benefit – extent: "considerable"	–
AE: adverse event; DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; VAS: visual analogue scale	

The summarizing assessment showed only positive effects of ixekizumab in the outcome categories "morbidity", "health-related quality of life" and "side effects".

In the category of non-serious/non-severe symptoms, there was an indication of considerable added benefit in comparison with the appropriate comparator therapy for the outcome "remission" (PASI 100). In addition, there were 2 hints with an extent that is at most "considerable". For the outcome category "health-related quality of life", there was a hint of considerable added benefit for the outcome "DLQI (0 or 1)". In the category of non-serious/non-severe side effects, there was an indication of considerable added benefit for the outcome "discontinuation due to AEs".

In summary, there is an indication of considerable added benefit for adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy.

2.1.4 List of included studies

Studie RHBZ

Eli Lilly and Company. A study of ixekizumab (LY2439821) in participants with moderate-to-severe plaque psoriasis naive to systemic treatment: full text view [online]. In: ClinicalTrials.gov. 08.12.2016 [Accessed: 13.03.2017]. URL: https://clinicaltrials.gov/show/NCT02634801.

Eli Lilly and Company. A 24-week multicenter, randomized, open-label, parallel group study comparing the efficacy and safety of ixekizumab to fumaric acid esters and methotrexate in patients with moderate-to-severe plaque psoriasis who are naive to systemic treatment [online]. In: EU Clinical Trials Register. [Accessed: 13.03.2017].

Eli Lilly and Company. A 24-week multicenter, randomized, open-label, parallel-group study comparing the efficacy and safety of ixekizumab to fumaric acid esters and methotrexate in patients with moderate-to-severe plaque psoriasis who are naïve to systemic treatment with an extension period: study I1F-EW-RHBZ; clinical protocol [unpublished]. 2016.

Eli Lilly and Company. A 24-week, multicenter, randomized, open-label, parallel-group study comparing the efficacy and safety of ixekizumab to fumaric acid esters and methotrexate in patients with moderate-to-severe plaque psoriasis who are naïve to systemic treatment with an extension period: study I1F-EW-RHBZ; clinical study report [unpublished]. 2017.

2.2 Assessment of the Nail Psoriasis Severity Index in the IXORAS study (research question B)

For research question B of the benefit assessment of ixekizumab (patients with plaque psoriasis with inadequate response to other systemic treatments or who are unsuitable for these treatments), the company included the IXORAS study in its dossier [9].

A detailed description and the assessment of the IXORAS study can be found in the dossier assessment on ixekizumab [1]. The company presented analyses for the assessment of nail psoriasis using NAPSI in its dossier. However, he had only included a subpopulation of the IXORAS study in the analyses, namely those patients with nail involvement at the start of the study. These were about 63% of the randomized patients. Recording of the nail psoriasis was rated as patient-relevant in the dossier assessment [1] and included in the assessment. However, the data presented by the company were rated as unusable since not all randomized patients were considered in the analysis and patients with newly occurring nail involvement in the course of the study would not have been recorded.

The G-BA commissioned IQWiG to assess the outcome "NAPSI" in patients with nail involvement at the start of the study. The corresponding results of the outcome are presented below. The operationalization as proportion of patients with a NAPSI score of 0 (equivalent to complete freedom of symptoms) at week 24. Table 9 shows the results for the outcome "NAPSI". The risk of bias for the outcome "NAPSI" was rated as low.

Table 9: Results (morbidity) – RCT, direct comparison: ixekizumab vs. ustekinumab

Study Outcome category Outcome	Ixekizumab		Ustekinumab		Ixekizumab vs. ustekinumab
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value
IXORAS					
Morbidity					
NAPSI score 0[b]	84	41 (51.3)	105	24 (24.7)	2.28 [1.27; 3.29]; 0.012

a: Number of patients included in the analysis, consisting of patients with NAPSI > 0 at the start of the study.
b: A NAPSI score of 0 indicates freedom of symptoms.
CI: confidence interval; n: number of patients with (at least 1) event; N: number of analysed patients; NAPSI: Nail Psoriasis Severity Index; RCT: randomized controlled trial; RR: relative risk; vs.: versus

For the outcome "NAPSI", there was a statistically significant difference in favour of ixekizumab in patients whose nails were found to be affected at the start of the study.

3 References

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ixekizumab (Plaque Psoriasis): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A17-07 [online]. 30.05.2017 [Accessed: 17.07.2017]. (IQWiG-Berichte; Volume 514). URL: https://www.iqwig.de/download/A17-07_Ixekizumab_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

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9. Lilly. Ixekizumab (Taltz): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4 B; erwachsene Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die auf andere systemische Therapien einschließlich Ciclosporin, Methotrexat oder PUVA [Psoralen und Ultraviolett A Licht] nur unzureichend angesprochen haben, oder bei denen eine Kontraindikation oder Unverträglichkeit gegenüber solchen Therapien vorliegt; medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen [online]. 24.02.2017 [Accessed: 19.07.2017]. URL: https://www.g-ba.de/downloads/92-975-1818/2017-02-24_Modul4B_Ixekizumab.pdf.

Appendix A – Results on side effects

Table 10: Common AEs (in the SOC and in the PT ≥ 3% in at least 1 study arm) – RCT, direct comparison: ixekizumab vs. fumaric acid esters or methotrexate (total population of study RHBZ)

Study	Patients with event n (%)					
SOC[a] PT[a]	Ixekizumab N = 54		Fumaric acid esters N = 52		Methotrexate N = 52	
RHBZ						
Overall rate of adverse events	46	(85.2)	46	(88.5)	43	(82.7)
Infections and infestations	30	(55.6)	14	(26.9)	25	(48.1)
Nasopharyngitis	21	(38.9)	9	(17.3)	18	(34.6)
Urinary tract infection	2	(3.7)	2	(3.8)	2	(3.8)
Gastroenteritis viral	1	(1.9)	1	(1.9)	2	(3.8)
Tinea pedis	2	(3.7)	0	(0)	1	(1.9)
Hordeolum	2	(3.7)	0	(0)	0	(0)
Gastrointestinal disorders	7	(13.0)	35	(67.3)	17	(32.7)
Diarrhoea	0	(0)	23	(44.2)	6	(11.5)
Upper abdominal pain	1	(1.9)	19	(36.5)	6	(11.5)
Nausea	1	(1.9)	3	(5.8)	5	(9.6)
Abdominal discomfort	2	(3.7)	2	(3.8)	1	(1.9)
Flatulence	0	(0)	3	(5.8)	0	(0)
Vomiting	0	(0)	3	(5.8)	0	(0)
Abdominal pain	0	(0)	1	(1.9)	2	(3.8)
Gastrointestinal disorders	0	(0)	2	(3.8)	0	(0)
General disorders and administration site conditions	16	(29.6)	5	(9.6)	9	(17.3)
Fatigue	4	(7.4)	3	(5.8)	8	(15.4)
Injection site reactions	7	(13.0)	0	(0)	0	(0)
Administration site pain	2	(3.7)	0	(0)	0	(0)
Oedema peripheral	0	(0)	0	(0)	2	(3.8)
Nervous system disorders	11	(20.4)	7	(13.5)	11	(21.2)
Headache	7	(13.0)	4	(7.7)	9	(17.3)
Dizziness	2	(3.7)	0	(0)	1	(1.9)
Musculoskeletal and connective tissue disorders	9	(16.7)	4	(7.7)	12	(23.1)
Back pain	1	(1.9)	2	(3.8)	5	(9.6)
Arthralgia	2	(3.7)	0	(0)	4	(7.7)

(continued)

Table 10: Common AEs (in the SOC and in the PT ≥ 3% in at least 1 study arm) – RCT, direct comparison: ixekizumab vs. fumaric acid esters or methotrexate (total population of study RHBZ) (continued)

Study	**Patients with event n (%)**					
SOC[a] **PT[a]**	**Ixekizumab N = 54**		**Fumaric acid esters N = 52**		**Methotrexate N = 52**	
Skin and subcutaneous tissue disorders	7	(13.0)	6	(11.5)	6	(11.5)
Pruritus	2	(3.7)	2	(3.8)	1	(1.9)
Psoriasis	1	(1.9)	1	(1.9)	2	(3.8)
Alopecia	2	(3.7)	0	(0)	1	(1.9)
Vascular disorders	2	(3.7)	14	(26.9)	1	(1.9)
Flushing	0	(0)	13	(25.0)	0	(0)
Investigations	6	(11.1)	7	(13.5)	3	(5.8)
Gamma-glutamyltransferase increase	0	(0)	3	(5.8)	0	(0)
Respiratory, thoracic and mediastinal disorders	6	(11.1)	3	(5.8)	3	(5.8)
Oropharyngeal pain	3	(5.6)	1	(1.9)	1	(1.9)
Cough	1	(1.9)	2	(3.8)	1	(1.9)
Injury, poisoning and procedural complications	5	(9.3)	1	(1.9)	6	(11.5)
Arthropod bite	0	(0)	0	(0)	3	(5.8)
Ear and labyrinth disorders	2	(3.7)	3	(5.8)	3	(5.8)
Dizziness	2	(3.7)	3	(5.8)	3	(5.8)
Blood and lymphatic system disorders	0	(0)	5	(9.6)	3	(5.8)
Lymphopenia	0	(0)	5	(9.6)	2	(3.8)
Lymphadenopathy	0	(0)	0	(0)	2	(3.8)
Metabolism and nutrition disorders	3	(5.6)	1	(1.9)	0	(0)
Decreased appetite	2	(3.7)	0	(0)	0	(0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(3.7)	0	(0)	1	(1.9)
Renal and urinary disorders	2	(3.7)	0	(0)	0	(0)
Eye disorders	0	(0)	0	(0)	2	(3.8)

a: MedDRA version 19.1.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus