IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ixekizumab (psoriatic arthritis) –

Addendum to Commission A18-14[1]

Addendum

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

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum:

- Natalia Wolfram
- Charlotte Guddat
- Volker Vervölgyi

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List of abbreviations

Abbreviation	Meaning
bDMARD	biologic disease-modifying antirheumatic drug
CASPAR	Classification for Psoriatic Arthritis
CSR	clinical study report
DMARD	disease-modifying antirheumatic drug
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LEI	Leeds Enthesitis Index
MMRM	mixed-effects model repeated measure
NRI	non-responder imputation
PASI	Psoriasis Area and Severity Index
RCT	randomized controlled trial
RR	relative risk

1 Background

On 9 July 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A18-14 (Ixekizumab – Benefit assessment according to §35a Social Code Book V [1]).

For the assessment of research question 2 (biologic disease-modifying antirheumatic drug [bDMARD]-naive patients with active psoriatic arthritis for whom a first treatment with bDMARDs is indicated), the pharmaceutical company (hereinafter referred to as "the company") presented results of the subpopulation of the randomized controlled trial (RCT) RHAP in its dossier. In this subpopulation, ixekizumab was compared with adalimumab in disease-modifying antirheumatic drug (DMARD)-pretreated patients without concomitant moderate to severe plaque psoriasis. The study was used for the benefit assessment.

The dossier assessment described uncertainties regarding the proportion of imputed values for the binary outcomes on morbidity and health-related quality of life. In its subsequent comment [2], the company presented information and analyses for research question B that went beyond the information provided in the dossier. The G-BA commissioned IQWiG with the assessment of these analyses under consideration of the information provided 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 Description of the initial data situation in the company's dossier

The RHAP study was a 4-arm RCT that compared 2 dosages of ixekizumab versus adalimumab or placebo in patients with active psoriatic arthritis according to the Classification for Psoriatic Arthritis (CASPAR) criteria. For the assessment of research question 2, the company presented results on the comparison of ixekizumab with adalimumab in the subpopulation of DMARD-pretreated patients without concomitant moderate to severe plaque psoriasis in its dossier.

The treatment duration in the relevant randomized study phase was 24 weeks. Patients with inadequate response at treatment week 16 (defined as < 20% decrease in tender and swollen joint count) were to receive rescue therapy. Patients in the ixekizumab arm with an inadequate response received rescue medication in addition to continued ixekizumab treatment. Patients in the adalimumab arm were switched to placebo and received only rescue medication until week 24. The proportion of patients for whom rescue therapy was an option was 7.8% in the ixekizumab arm and 8.9% in the adalimumab arm. The detailed characteristics of this study and of the corresponding subpopulation can be found in dossier assessment A18-14 [1].

Various outcomes on benefit and harm were included in the assessment of the added benefit of ixekizumab in comparison with adalimumab (see Table 10 in dossier assessment A18-14 [1]). The relative risk (RR) presented by the company was used for dichotomous outcomes. For continuous outcomes, which were operationalized as change from baseline, the mean difference from the analysis using a mixed-effects model repeated measures (MMRM) presented by the company was used.

Based on the information from Module 4 A and from the clinical study report (CSR), it was assumed that the company had used the following methods for its analyses for handling the values in its dossier:

- It was assumed for dichotomous outcomes that the company had rated missing values as non-responses (non-responder imputation [NRI] analysis). It was also assumed that patients who were candidates for rescue medication in week 16 due to non-response to the treatment had been rated as non-responders. However, the company presented no information on the proportion of imputed values in the dossier. A high risk of bias was therefore derived in the benefit assessment for the results of dichotomous outcomes.
- It was assumed for continuous outcomes that the values of the patients who were candidates for rescue medication in week 16 had been rated as missing from this time point. In the dossier, the company provided no information on the exact number of patients included in the respective analysis. Based on the information provided on the number of patients with complete recording per documentation time, a low risk of bias was derived for these outcomes, however.

The uncertainties regarding the proportion of imputed values and the actual number of patients included in the analysis, as well as the resulting consequences, were described in the benefit assessment [1].

2.2 Assessment of the analyses submitted by the company with the comment

Description of the analyses presented

In its written comment, the company addressed the statistical methods used in the dossier and described how it had considered the values of patients who were candidates for rescue medication in week 16 due to non-response to the treatment. According to the company, these patients in the ixekizumab arm were included with their actually observed values in the respective analysis. The values of patients in the adalimumab arm, however – in contrast to the assumption described in the previous section and different from the ixekizumab arm – were assumed to be non-responders (dichotomous efficacy outcomes) or their values after week 16 were assumed to be missing (continuous outcomes). Despite the criticism in the dossier assessment, the company provided subsequent information on the number of values imputed by the company only for the outcomes based on the Psoriasis Area and Severity Index (PASI). The number of patients included in the MMRM analyses of continuous outcomes was not addressed at all by the company.

Firstly, it should be noted that the company's dossier did not clearly describe the differences in the way the company handled the values of patients who were candidates for rescue medication in week 16. As described above, it was assumed despite uncertainties that the company, analogous to the approach described in the study documents for the total population, had imputed the values in its analyses for the subpopulation or had assumed them to be missing. There was a systematic difference between the study arms in the way the company handled the values for the analyses for the subpopulation, which was neither predefined nor meaningful with regard to content.

With its comment, the company presented new analyses for the following outcomes: enthesitis (measured with the Leeds Enthesitis Index [LEI]), tender and swollen joint count, skin symptoms analysed with the PASI 100 and additionally with the outcomes "PASI 75" and "PASI 90" presented in the dossier assessment. In these analyses, which it referred to as sensitivity analyses, the values of the patients mentioned above were handled in the same way in both study arms, i. e. assumed as non-response for binary outcomes and as missing for continuous outcomes. This concurs with the analyses originally planned in the study. Against this background, an assessment of the analyses subsequently submitted is meaningful.

However, the company restricted its analyses only to the outcomes based on which an added benefit had been derived in the dossier assessment. Restricting the analyses to a choice of outcomes is inadequate. Instead, the company should have provided new analyses for all outcomes on morbidity and health-related quality of life, or should have at least discussed to what extent the results of the analyses change due to the different handling. This is of particular

importance against the background that the results presented by the company show that the way the values of patients who were candidates for rescue medication in week 16 were handled had a relevant influence on the results (see section on results below).

Results on added benefit

High risk of bias of the results for the outcomes on morbidity and health-related quality of life

As described above, the company presented selective analyses for a choice of outcomes. The information on the imputation of missing values for PASI 100 subsequently submitted additionally show that the values were imputed to a relevant extent (see Table 1). Despite criticism in the report, the company provided no information on imputed values or on the number of patients included in the MMRM analysis regarding further outcomes on morbidity and health-related quality of life. This selective presentation by the company resulted in the high risk of bias of the results for all outcomes on morbidity and health-related quality of life.

Hence, the assessment of the risk of bias for the outcomes on morbidity and health-related quality of life changed in comparison with assessment A18-14 [1]. A low risk of bias of the results was still assumed for the outcomes on mortality and side effects.

Results

Hereinafter, Table 1 and Table 2 present the results subsequently submitted by the company on the outcomes chosen by the company on the comparison of ixekizumab with adalimumab in patients with active psoriatic arthritis who are candidates for treatment with a bDMARD for the first time. The description of the results for these outcomes contains information on whether the results of the assessment have changed in comparison with the dossier assessment.

See Table 12 and Table 13 of dossier assessment A18-14 [1] for the results for further relevant outcomes.

Table 1: Results on morbidity (dichotomous) – RCT, direct comparison: ixekizumab vs. adalimumab

Study Outcome category Outcome	Ixekizumab N	Ixekizumab Patients with event n (%)	Adalimumab N	Adalimumab Patients with event n (%)	Ixekizumab vs. adalimumab RR [95% CI]; p-value[a]
RHAP					
Morbidity					
Skin symptoms[b]					
Remission (PASI 100)[c]	51	21 (41.2)	56	12 (21.4)	1.92 [1.06; 3.50]; 0.029
PASI 90 (additional information)	*51*	*26 (51.0)*	*56*	*14 (25.0)*	*2.04 [1.20; 3.46]; 0.006*
PASI 75 (additional information)	*51*	*28 (54.9)*	*56*	*20 (35.7)*	*1.54 [1.00; 2.36]; 0.0505*

a: Institute's calculation (unconditional exact test, CSZ method according to [3]).
b: Patients with missing values were imputed as non-responders in analyses for outcomes on skin symptoms. Values of patients who were candidates for rescue medication in week 16 were also imputed as non-responders.
c: The total proportion of imputed values was 31.4% in the ixekizumab arm and 16.1% in the adalimumab arm. The proportion of imputed values due to the possible administration of rescue medication was 7.8% in the ixekizumab arm and 8.9% in the adalimumab arm.

CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 2: Results on morbidity (continuous) – RCT, direct comparison: ixekizumab vs. adalimumab

Study Outcome category	Ixekizumab			Adalimumab			Ixekizumab vs. adalimumab
Outcome	**N[a]**	**Values at study start mean (SD)**	**Change at end of study mean[b] (SE)**	**N[a]**	**Values at study start mean (SD)**	**Change at end of study mean[b] (SE)**	**MD [95% CI]; p-value[b]**
RHAP							
Morbidity							
Enthesitis (LEI)[c]	ND	1.4 (1.68)	−0.90 (0.20)	ND	1.5 (1.90)	−0.30 (0.20)	−0.60 [−1.08; −0.12]; 0.014
Tender joint count[c]	ND	19.00 (13.10)	−12.88 (1.39)	ND	17.54 (12.88)	−10.57 (1.34)	−2.31 [−5.76; 1.13]; 0.184
Swollen joint count[c]	ND	10.61 (7.97)	−6.99 (0.72)	ND	9.30 (6.48)	−5.89 (0.70)	−1.10 [−2.90; 0.69]; 0.225

a: Values of patients who were candidates for rescue medication in week 16 were assumed as missing from week 16.
b: Changes at the end of study in comparison with baseline and mean differences from MMRM analysis. Based on the information provided in the company's comment and dossier, it was assumed that the model contained terms for treatment, visit, geographical region and csDMARD experience, the baseline value as covariate and visit by treatment interaction.
c: Negative changes indicate improvement; a negative mean difference indicates an advantage of ixekizumab.
CI: confidence interval; csDMARD: conventional synthetic disease-modifying antirheumatic drug; LEI: Leeds Enthesitis Index; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

Skin symptoms (PASI 100)

The company's analysis with imputation of the data using NRI, as well as dossier assessment A18-14 [1], showed a statistically significant difference in favour of ixekizumab in comparison with adalimumab for the outcome "skin symptoms" recorded with the PASI 100. The Institute's calculation of the RR (reversed direction of effect) to enable use of limits to derive the extent of the added benefit [4] resulted in an RR (95% confidence interval] of 0.52 [0.29; 0.95] for the outcome "PASI 100". In contrast to the result from dossier assessment A18-14, the effect for PASI 100, which is to be allocated to the category of non-serious/non-severe symptoms/late complications, is therefore no more than marginal. This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab for the outcome "PASI 100"; an added benefit is therefore not proven.

Enthesitis (LEI)

For the outcome "enthesitis (LEI)", a statistically significant difference in favour of ixekizumab was shown for the change from baseline in the number of tender entheses, as was the case in dossier assessment A18-14 [1]. As shown above, there was a high risk of bias of the results for this outcome. In addition, the relevance of this effect (the 95% confidence interval of the effect

was [0.12; 1.08] entheses) cannot be estimated with certainty. This resulted in a hint of an added benefit of ixekizumab in comparison with adalimumab for the outcome "enthesitis". Concurring with the approach described in the dossier assessment, the extent of the added benefit was rated as low.

Tender and swollen joint count

In contrast to the dossier assessment [1], no statistically significant difference between ixekizumab and adalimumab was shown for each of the outcomes "tender and swollen joint count" for the change from baseline. This resulted in no hint of an added benefit of ixekizumab in comparison with adalimumab for these outcomes; an added benefit is therefore not proven.

2.3 Overall consideration of the results and overall conclusion on the added benefit

Table 3 shows the changes in the positive effects from the dossier assessment on ixekizumab in comparison with adalimumab under consideration of the analyses assessed in the addendum.

Table 3: Positive and negative effects from the assessment of ixekizumab in comparison with adalimumab under consideration of the addendum

Positive effects from dossier assessment A18-14	**Changes in the positive effects under consideration of the addendum**
Outcome category: non-serious/non-severe symptoms/late complications:	
▪ skin symptoms (PASI 100): hint of an added benefit – extent: "minor" ▪ enthesitis: hint of an added benefit – extent "minor" ▪ tender/swollen joint count: in each case hint of an added benefit – extent "minor"	▪ skin symptoms (PASI 100): lesser benefit/added benefit not proven ▪ enthesitis: hint of an added benefit – extent "minor" ▪ Tender/swollen joint count: in each case lesser benefit/added benefit not proven
Negative effects in the outcome category "non-serious/non-severe side effects" are unchanged:	
▪ specific AEs (general disorders and administration site conditions): indication of greater harm – extent "considerable"	
AE: adverse event; PASI: Psoriasis Area and Severity Index	

The comparison of the results of the analyses subsequently submitted by the company, which assumed values of patients who were candidates for rescue medication in week 16 as non-response or missing, versus the results of the analyses originally presented by the company, which handled the values of patients who were candidates for rescue medication in week 16 differently depending on the study arm, showed that the way the values were handled had a relevant influence on the results:

In contrast to dossier assessment A18-14, the positive effect of ixekizumab only remains for the outcome "enthesitis" when the same imputation strategy (NRI) is used for both study arms. The positive effects for further outcomes were no longer shown, however, or their extent was no more than marginal. In contrast, there was still an indication of greater harm of ixekizumab

with the extent "considerable" for the outcome "general disorders and administration site conditions".

In the overall consideration of the data, there is no hint of an added benefit of ixekizumab in comparison with adalimumab.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure changed the conclusion on the added benefit of ixekizumab from dossier assessment A18-14 for research question 2: The added benefit of ixekizumab for bDMARD-naive patients with active psoriatic arthritis for whom a first treatment with bDMARDs is indicated is not proven. For the other research questions, there was no change in comparison with dossier assessment A18-14.

The following Table 4 shows the result of the benefit assessment of ixekizumab under consideration of dossier assessment A18-14 and the present addendum.

Table 4: Ixekizumab – probability and extent of added benefit

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

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Changes in comparison with dossier assessment A18-14 are printed in **bold**.
c: Poor prognostic factors: ≥ 5 affected joints; radiographic joint damage; increased inflammatory markers; extraarticular manifestations, particularly dactylitis.
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ixekizumab (Psoriasis Arthritis): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A18-14 [online]. 30.05.2018 [Accessed: 22.06.2018]. (IQWiG-Berichte; Volume 631). URL: https://www.iqwig.de/download/A18-14_Ixekizumab_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. Lilly Deutschland. Stellungnahme zum IQWiG-Bericht Nr. 631: Ixekizumab (Psoriasis Arthritis); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A18-14. [Soon available under https://www.g-ba.de/informationen/nutzenbewertung/350/#beschluesse in the document "Zusammenfassende Dokumentation"].

3. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

4. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf