IQWiG Reports – Commission No. A19-87

Risankizumab (plaque psoriasis) –

Addendum to Commission A19-41[1]

Addendum

Commission: A19-87
Version: 1.0
Status: 30 October 2019

[1] Translation of addendum A19-87 *Risankizumab (Plaque-Psoriasis) – Addendum zum Auftrag A19-41* (Version 1.0; Status: 30 October 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Risankizumab (plaque psoriasis) – Addendum to Commission A19-41

Commissioning agency
Federal Joint Committee

Commission awarded on
7 October 2019

Internal Commission No.
A19-87

Address of publisher
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Keywords: risankizumab, psoriasis, benefit assessment, NCT02684357, NCT02684370

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List of abbreviations

Abbreviation	Meaning
DLQI	Dermatology Life Quality Index
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
MI	multiple imputation
NRI	non-responder imputation
PASI	Psoriasis Area and Severity Index
PSS	Psoriasis Symptom Scale
PSSI	Psoriasis Scalp Severity Index
RCT	randomized controlled trial

1 Background

On 7 October 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-41 (Risankizumab – Benefit assessment according to §35a Social Code Book V) [1].

The 2 randomized controlled trials (RCTs) UltIMMa-1 and UltIMMa-2 were used for the benefit assessment of risankizumab in adult patients with moderate to severe plaque psoriasis with inadequate response or intolerance to systemic therapy.

With its written comments to the dossier assessment [2,3], the pharmaceutical company (hereinafter referred to as "the company") provided sensitivity analyses for the following outcomes: itching, pain, redness and burning of the Psoriasis Symptom Scale (PSS), as well as absence of symptoms on the scalp (Psoriasis Scalp Severity Index [PSSI]) and health-related quality of life (Dermatology Life Quality Index [DLQI]). The G-BA commissioned IQWiG to assess these sensitivity analyses.

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 data situation

The 2 RCTs UltIMMa-1 and UltIMMa-2 were used for the benefit assessment of risankizumab in adult patients with moderate to severe plaque psoriasis with inadequate response or intolerance to systemic therapy (research question B of dossier assessment A19-41). These studies compared risankizumab with ustekinumab.

In the assessment, the results on the symptom outcomes (Psoriasis Area and Severity Index [PASI] and PSS outcomes itching, pain, redness and burning) and on health-related quality of life (DLQI) were rated as having a high risk of bias. This was due to the large and differential proportions of patients imputed using non-responder imputation (NRI) [1]. The company's dossier contained 2 sensitivity analyses for the PASI 100 [4]. These were the sensitivity analyses with imputation of missing values by last observation carried forward (LOCF) and multiple imputation (MI) planned in the studies. In comparison with the primary NRI analysis, the results of the sensitivity analyses showed consistent effects of comparable magnitude. Despite high risk of bias, the certainty of results was not downgraded for this outcome, and proof of an added benefit was derived.

With its comments, the company now subsequently submitted the described sensitivity analyses (LOCF and MI) also for the further responder analyses on symptoms and on health-related quality of life. For the PSS outcomes (itching, pain, redness and burning) and the DLQI, these are presented below, and the effects on the outcome-specific certainty of conclusions are assessed.

The company subsequently submitted these sensitivity analyses also for the outcome "PSSI". However, the high risk of bias for this outcome was mainly due to the fact that the analyses only comprised patients with PSSI > 0 at baseline, which resulted in high and differential proportions of missing patients (risankizumab versus ustekinumab: UltIMMa-1 9% versus 14.7%; UltIMMa-2 11.1% versus 22.2% [1]). In this situation, the presented sensitivity analyses with different imputation strategies are unsuitable to address the problem of the high risk of bias. For this outcome, no assessment of the certainty of conclusions that differs from the original benefit assessment can therefore be derived from the sensitivity analyses, which are not presented below.

Subgroup analyses

The company presented the sensitivity analyses only for the total relevant subpopulations of the studies UltIMMa-1 and UltIMMa-2. For the PSS outcomes (itching, pain, redness and burning), however, the NRI analysis showed effect modifications by age (itching, pain and burning) and by previous biologic treatment (redness). The company did not present any subgroup analyses for these outcomes for the sensitivity analyses (LOCF and MI), however. Therefore, when interpreting the results of the sensitivity analyses, an additional outcome-specific assessment is

made as to whether the lack of the sensitivity analyses for the subgroup analyses affects the assessment of the certainty of conclusions in the respective subgroup.

2.2 Results

Table 1 shows the results on the 4 PSS outcomes (itching, pain, redness and burning) and the DLQI for the total relevant subpopulation with the different imputation strategies (main analysis: imputation using NRI, supplementary information: imputation strategies using LOCF and MI). The presented results of the main analysis concur with those of dossier assessment A19-41.

Table 1: Results (morbidity, health-related quality of life, dichotomous) – RCT, direct comparison: risankizumab vs. ustekinumab (research question B)

Outcome category **Outcome** **Time point** **Study**	**Risankizumab** **N**	**Risankizumab** **Patients with event n (%)**	**Ustekinumab** **N**	**Ustekinumab** **Patients with event n (%)**	**Risankizumab vs. ustekinumab** **RR [95% CI][a]; p-value**
Week 52					
Morbidity					
Skin symptoms					
Patient-reported absence of symptoms PSS itching 0[b]					
UltIMMa-1	100	69 (69.0)	34	13 (38.2)	1.76 [1.13; 2.75]; 0.013
UltIMMa-2	90	67 (74.4)	36	14 (38.9)	1.90 [1.25; 2.90]; 0.003
Total					1.85 [1.36; 2.51]; < 0.001
PSS itching 0 – sensitivity analysis (LOCF), supplementary information[c]					
UltIMMa-1	*100*	*71 (71.0)*	*33*	*14 (42.4)*	*1.62 [1.07; 2.46]; 0.023*
UltIMMa-2	*90*	*69 (76.7)*	*36*	*16 (44.4)*	*1.73 [1.18; 2.52]; 0.005*
Total[d]					*1.69 [1.28; 2.24]; < 0.001*
PSS itching 0 – sensitivity analysis (MI), supplementary information[e]					
UltIMMa-1	*100*	*69.30 (69.3)*	*33*	*13.05 (39.5)*	*1.70 [1.09; 2.65]; 0.019*
UltIMMa-2	*90*	*67.15 (74.6)*	*36*	*13.30 (36.9)*	*2.01 [1.29; 3.14]; 0.002*
Total[d]					*1.88 [1.37; 2.57]; < 0.001*

(continued)

Table 1: Results (morbidity, health-related quality of life, dichotomous) – RCT, direct comparison: risankizumab vs. ustekinumab (research question B) (continued)

Outcome category **Outcome** **Time point** **Study**	**Risankizumab** **N**	**Risankizumab** **Patients with event n (%)**	**Ustekinumab** **N**	**Ustekinumab** **Patients with event n (%)**	**Risankizumab vs. ustekinumab** **RR [95% CI][a]; p-value**
PSS pain 0[b]					
UltIMMa-1	100	82 (82.0)	34	17 (50.0)	1.59 [1.13; 2.25]; 0.008
UltIMMa-2	90	75 (83.3)	36	21 (58.3)	1.41 [1.06; 1.88]; 0.018
Total					1.49 [1.20; 1.86]; < 0.001
PSS pain 0 – sensitivity analysis (LOCF), supplementary information[c]					
UltIMMa-1	*100*	*85 (85.0)*	*33*	*18 (54.5)*	*1.50 [1.08; 2.08]; 0.014*
UltIMMa-2	*90*	*77 (85.6)*	*36*	*24 (66.7)*	*1.28 [1.01; 1.63]; 0.045*
Total[d]					*1.37 [1.13; 1.67] 0.002*
PSS pain 0 – sensitivity analysis (MI), supplementary information[e]					
UltIMMa-1	*100*	*82.65 (82.7)*	*33*	*17.05 (51.7)*	*1.54 [1.09; 2.17]; 0.014*
UltIMMa-2	*90*	*75.30 (83.7)*	*36*	*20.80 (57.8)*	*1.44 [1.07; 1.95]; 0.018*
Total[d]					*1.49 [1.19; 1.87]; < 0.001*

(continued)

Table 1: Results (morbidity, health-related quality of life, dichotomous) – RCT, direct comparison: risankizumab vs. ustekinumab (research question B) (continued)

Outcome category **Outcome** **Time point** **Study**	**Risankizumab**		**Ustekinumab**		**Risankizumab vs. ustekinumab**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI][a]; p-value**
PSS redness 0[b]					
UltIMMa-1	100	68 (68.0)	34	12 (35.3)	1.97 [1.23; 3.16]; 0.005
UltIMMa-2	90	68 (75.6)	36	15 (41.7)	1.82 [1.22; 2.71]; 0.003
Total					1.85 [1.37; 2.52]; < 0.001
PSS redness 0 – sensitivity analysis (LOCF), supplementary information[c]					
UltIMMa-1	*100*	*70 (70.0)*	*33*	*12 (36.4)*	*1.97 [1.23; 3.15]; 0.005*
UltIMMa-2	*90*	*70 (77.8)*	*36*	*18 (50.0)*	*1.55 [1.10; 2.17]; 0.011*
Total[d]					*1.67 [1.27; 2.21]; < 0.001*
PSS redness 0 – sensitivity analysis (MI), supplementary information[e]					
UltIMMa-1	*100*	*68.30 (68.3)*	*33*	*12.00 (36.4)*	*1.91 [1.19; 3.07]; 0.007*
UltIMMa-2	*90*	*68.20 (75.8)*	*36*	*15.20 (42.2)*	*1.80 [1.21; 2.68]; 0.004*
Total[d]					*1.82 [1.34; 2.47]; < 0.001*

(continued)

Table 1: Results (morbidity, health-related quality of life, dichotomous) – RCT, direct comparison: risankizumab vs. ustekinumab (research question B) (continued)

Outcome category **Outcome** **Time point** **Study**	**Risankizumab**		**Ustekinumab**		**Risankizumab vs. ustekinumab**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI][a]; p-value**
PSS burning 0[b]					
UltIMMa-1	100	85 (85.0)	34	23 (67.6)	1.26 [0.98; 1.61]; 0.070[f]
UltIMMa-2	90	77 (85.6)	36	21 (58.3)	1.47 [1.10; 1.96]; 0.009
Total					1.34 [1.11; 1.63]; 0.002
PSS burning 0 – sensitivity analysis (LOCF), supplementary information[c]					
UltIMMa-1	*100*	*88 (88.0)*	*33*	*24 (72.7)*	*1.21 [0.97; 1.51]; 0.091[f]*
UltIMMa-2	*90*	*79 (87.8)*	*36*	*26 (72.2)*	*1.22 [0.98; 1.51]; 0.075*
Total[d]					*1.20 [1.03; 1.41]; 0.022*
PSS burning 0 – sensitivity analysis (MI), supplementary information[e]					
UltIMMa-1	*100*	*85.30 (85.3)*	*33*	*23.10 (70.0)*	*1.13 [0.92; 1.38]; 0.240*
UltIMMa-2	*90*	*77.60 (86.2)*	*36*	*20.55 (57.1)*	*1.52 [1.12; 2.05]; 0.007*
Total[d]					*1.34 [1.11; 1.63]; 0.003*

(continued)

Table 1: Results (morbidity, health-related quality of life, dichotomous) – RCT, direct comparison: risankizumab vs. ustekinumab (research question B) (continued)

Outcome category **Outcome** **Time point** **Study**	**Risankizumab** **N**	**Risankizumab** **Patients with event n (%)**	**Ustekinumab** **N**	**Ustekinumab** **Patients with event n (%)**	**Risankizumab vs. ustekinumab** **RR [95% CI][a]; p-value**
Health-related quality of life					
DLQI (0 or 1)[b]					
UltIMMa-1	100	75 (75.0)	34	19 (55.9)	1.30 [0.96; 1.75]; 0.089
UltIMMa-2	90	69 (76.7)	36	17 (47.2)	1.63 [1.14; 2.34]; 0.008
Total[d]					1.47 [1.16; 1.86]; 0.001
DLQI (0 or 1)– sensitivity analysis (LOCF), supplementary information[c]					
UltIMMa-1	*99*	*78 (78.8)*	*33*	*20 (60.6)*	*1.24 [0.95; 1.62]; 0.116*
UltIMMa-2	*90*	*72 (80.0)*	*35*	*19 (54.3)*	*1.47 [1.07; 2.03]; 0.018*
Total[d]					*1.38 [1.11; 1.71]; 0.003*
DLQI (0 or 1) – sensitivity analysis (MI), supplementary information[e]					
UltIMMa-1	*100*	*76.10 (76.1)*	*33*	*19.25 (58.3)*	*1.25 [0.93; 1.67]; 0.137*
UltIMMa-2	*90*	*69.95 (77.7)*	*36*	*17.90 (49.7)*	*1.57 [1.10; 2.25]; 0.013*
Total[d]					*1.42 [1.12; 1.79]; 0.003*

a: RR and CI from generalized linear model with treatment and stratification variables as covariables with a log link for the calculation of the RR. For the meta-analysis, the variable study was additionally included in the model as a fixed effect.
b: Missing values imputed using NRI.
c: Missing values imputed using LOCF.
d: Calculated from IPD meta-analysis with fixed effect.
e: Missing values imputed using MI.
f: Model did not converge, so the model was calculated without stratification variables.
CI: confidence interval; DLQI: Dermatology Life Quality Index; IPD: individual patient data; LOCF: last observation carried forward; MI: multiple imputation; N: number of analysed patients; n: number of patients with (at least one) event; NRI: non-responder imputation; PSS: Psoriasis Symptom Scale; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Taking into account the sensitivity analyses now available, the following outcome-specific assessments are made regarding the certainty of conclusions and the extent of the added benefit.

PSS (itching, pain, redness)

For each of the outcomes “PSS itching”, “PSS pain” and “PSS redness”, the meta-analysis of the total population showed a statistically significant difference in favour of risankizumab with considerable extent (itching and redness) or minor extent (pain) in the benefit assessment. The results of the sensitivity analyses (LOCF and MI) now available also show a statistically significant advantage of risankizumab of comparable magnitude for each of the outcomes. The results are therefore robust, so that, despite the high risk of bias, a high certainty of results is assumed with regard to the total population. The benefit assessment showed an effect modification for the 3 outcomes, however: for the outcomes “itching” and “pain” by the characteristic “age”, for the outcome “redness” depending on previous biologic treatment.

For the outcomes “itching” and “pain”, an indication of considerable added benefit was derived in the benefit assessment only in the age group of patients between 40 and 64 years; there was no hint of an added benefit for the other age groups. Since for each of both outcomes, the effect in the subgroup of patients between 40 and 64 years of age was even greater than in the total population, and this subgroup constitutes a large proportion of the total population, a high certainty of results can also be derived for the subgroup in the present data situation. This results in proof of considerable added benefit for patients between 40 and 64 years of age for both outcomes.

For the outcome “redness”, the benefit assessment derived an indication of considerable added benefit only for the group of patients with previous biologic treatment; there was no hint of an added benefit for patients without previous biologic treatment. The present data situation is comparable to the situation regarding the outcome “itching”. Hence, there is proof of considerable added benefit for patients with previous biologic treatment.

PSS burning

The meta-analysis showed a statistically significant difference in favour of risankizumab for the outcome “PSS burning” in the benefit assessment. This difference was no more than marginal, however. The results of the sensitivity analyses (LOCF and MI) now available show a statistically significant advantage of risankizumab, which in each case is also no more than marginal. The benefit assessment also showed an effect modification by the characteristic “age” for the outcome.

For the outcome “PSS burning”, an indication of minor added benefit was derived only in the age group of patients between 40 and 64 years; there was no hint of an added benefit for the other age groups. The effect in the total population and in the subgroup of patients between 40 and 64 years of age on the basis of the NRI analysis is not large enough to assume a high certainty of results for this subgroup. Hence, there is still an indication of a minor added benefit for this outcome for patients between 40 and 64 years of age.

DLQI (0 or 1)

The meta-analysis showed an indication of considerable added benefit for the outcome "health-related quality of life", measured with the DLQI, in the benefit assessment. The results of the sensitivity analyses (LOCF and MI) now available show a statistically significant advantage of risankizumab of comparable magnitude. The result is therefore robust, so that a high certainty of results is assumed despite the high risk of bias. Hence, there is proof of considerable added benefit for this outcome.

2.3 Overall conclusion on added benefit

The following Table 2 shows the positive and negative effects from the assessment of risankizumab in comparison with ustekinumab on the basis of dossier assessment A19-41 and the present addendum.

Table 2: Positive and negative effects from the assessment of risankizumab in comparison with ustekinumab (research question B)

Positive effects[a]	**Negative effects**
Morbidity – non-serious/non-severe symptoms/late complications ▪ remission (PASI 100): proof of added benefit – extent: "considerable" ▪ absence of symptoms on the scalp (PSSI 0): indication of an added benefit – extent: "minor" ▪ patient-reported absence of symptoms (PSS itching 0) ▫ age ≥ 40 – < 65 years: **proof of** an added benefit – extent: "considerable" ▪ patient-reported absence of symptoms (PSS pain 0) ▫ age ≥ 40 – < 65 years: **proof of** an added benefit – extent: "considerable" ▪ patient-reported absence of symptoms (PSS burning 0) ▫ age ≥ 40 – < 65 years: indication of an added benefit – extent: "minor" ▪ patient-reported absence of symptoms (PSS redness 0) ▫ previous biologic treatment (yes): **proof of** an added benefit – extent: "considerable" ▪ health status (EQ-5D VAS) ▫ men: indication of an added benefit – extent: "non-quantifiable"	–
Health-related quality of life ▪ DLQI (0 or 1): **proof of** an added benefit – extent: "considerable"	–
a: Changes in comparison with the dossier assessment are printed in bold. DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life-5 Dimensions; PASI: Psoriasis Area and Severity Index; PSS: Psoriasis Symptom Scale; PSSI: Psoriasis Scalp Severity Index; VAS: visual analogue scale	

2.4 Summary

The data subsequently submitted by the company in the commenting procedure for research question B changed the certainty of conclusions at the level of individual outcomes, but they

did not change the overall conclusion on the added benefit of risankizumab from dossier assessment A19-41.

The following Table 3 shows the result of the benefit assessment of risankizumab under consideration of dossier assessment A19-41 and the present addendum.

Table 3: Risankizumab – probability and extent of added benefit

Research question	**Subindication**	**ACT[a]**	**Probability and extent of added benefit**
A	Adult patients with moderate to severe plaque psoriasis who are not candidates for conventional treatment in the framework of initial systemic therapy	Adalimumab or guselkumab or ixekizumab or secukinumab	Added benefit not proven
B	Adult patients with moderate to severe plaque psoriasis with inadequate response or intolerance to systemic therapy	Adalimumab or guselkumab or infliximab or ixekizumab or secukinumab or **ustekinumab**	Proof of considerable added benefit
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee			

The G-BA decides on the added benefit.

3 References

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

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