IQWiG Reports – Commission No. A21-156

Risankizumab (psoriatic arthritis) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Risankizumab (Psoriasis-Arthritis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 21 February 2022). Please note: This document was translated by an external translator and 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 (psoriatic arthritis) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
1 December 2021

Internal Commission No.
A21-156

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IQWiG thanks the medical and scientific advisor for her contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by 2 people.

IQWiG thanks the respondents for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondents were not involved in the actual preparation of the dossier assessment.

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Keywords: Risankizumab, Arthritis – Psoriatic, Benefit Assessment, NCT02684370, NCT02684357

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[2] 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
bDMARD	biologic disease-modifying antirheumatic drug
CASPAR	Classification for Psoriatic Arthritis
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)
MTX	methotrexate
PASI	Psoriasis Area and Severity Index
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
sPGA	static Physician Global Assessment
TNF	tumour necrosis factor

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 risankizumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 December 2021.

Research question

The aim of the present report is to assess the added benefit of risankizumab, either as monotherapy or in combination with methotrexate (MTX), versus the appropriate comparator therapy (ACT) in adult patients with active psoriatic arthritis who have experienced inadequate response or intolerance to prior therapy with disease-modifying antirheumatic drugs (DMARDs).

The ACT specified by the G-BA differs depending on the patient's pretreatment. The resulting research questions are shown in Table 2.

Table 2: Research questions of the benefit assessment of risankizumab

Research question	Therapeutic indication	ACT[a]
1	Adults with active psoriatic arthritis who have experienced inadequate response or intolerance to prior therapy with a DMARD[b]	A TNF-alpha antagonist (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an interleukin inhibitor (ixekizumab or secukinumab or ustekinumab), if applicable in combination with methotrexate
2	Adults with active psoriatic arthritis who have experienced inadequate response or intolerance to prior therapy with bDMARDs	Switch to another biologic disease-modifying antirheumatic drug (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab or ustekinumab), if applicable in combination with methotrexate

a. Presented is the respective ACT specified by the G-BA.
b. The patient population for research question 1 consists of bDMARD-naive patients.

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 company followed the G-BA's specification of the ACT. Overall, the company has drawn its conclusion on added benefit for the entire target population without asserting separate conclusions for the respective subpopulations for research questions 1 and 2. In line with the G-BA's specification, the present assessment attempted to answer the 2 research questions, each in comparison with the ACT specified by the G-BA. Since no usable data were available

for either of the two subpopulations designated by the G-BA, both research questions are assessed below in joint sections of the report.

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 deriving added benefit.

Study pool and study characteristics

For its benefit assessment, the company submitted the UltlMMa-1 and UltlMMa-2 studies. These studies had already been included in the first assessment of risankizumab in patients with plaque psoriasis (IQWiG assessment A19-41, Addendum A19-87).

The UltIMMa-1 and UltIMMa-2 studies are randomized, double-blind, parallel-group studies with identical protocols (twin studies) conducted in 79 and 64 study sites worldwide. The studies investigated risankizumab in comparison with placebo and ustekinumab in adults with moderate to severe plaque psoriasis. While the presence of psoriatic arthritis was not a prerequisite for inclusion in the studies, patients who had psoriatic arthritis in addition to plaque psoriasis were eligible for study inclusion. Patients with a prior history of or suspected psoriatic arthritis were evaluated according to Classification for Psoriatic Arthritis (CASPAR) criteria at selected study sites, and further surveys were conducted if psoriatic arthritis was confirmed.

The UltIMMa-1 study included a total of 506 patients, and the UltIMMa- study, 491 patients. In each study, patients were randomly allocated in a 3:1:1 ratio to the study arms of risankizumab (UltIMMa-1: N = 304; UltIMMa-2: N = 294), ustekinumab (UltIMMa-1: N = 100; UltIMMa-2: N = 99), and placebo (UltIMMa-1: N = 102; UltIMMa-: N = 98). Both studies stratified by the factors of body weight (≤ 100 kg versus > 100 kg) and prior treatment with tumour necrosis factor (TNF) antagonists (0 versus ≥ 1).

The primary outcomes of both studies were Psoriasis Area and Severity Index (PASI) 90 and a static Physician Global Assessment (sPGA) value of 0 or 1 at Week 16. Secondary outcomes were all-cause mortality, outcomes of the morbidity and health-related quality of life categories as well as adverse events (AEs).

No data available for the relevant subpopulations

The relevant population for the present benefit assessment is UltlMMa-1 and UltlMMa-2 participants who simultaneously exhibit both moderate to severe plaque psoriasis and active psoriatic arthritis. In addition, patients had to have received prior treatment with at least 1 DMARD, with said treatment having been inadequate or not tolerated. For this subpopulation, concrete information on the prior treatment received is also required to allow drawing separate conclusions for the patient populations for research question 1 (patients without prior biologic disease-modifying antirheumatic drug [bDMARD] treatment) and research question 2 (bDMARD-experienced patients).

From both studies, the company submitted analyses on the subpopulation of patients who have active psoriatic arthritis according to CASPAR criteria. The company did not further restrict this subpopulation to patients who had received prior treatment with at least 1 DMARD. Consequently, the subpopulation formed by the company was not categorized by the same in terms of prior therapy received, thus providing no separate data for bDMARD-naive patients (research question 1) versus bDMARD-experienced patients (research question 2).

Overall, this absence of information on prior treatment means that no adequate operationalization of the subpopulations for the 2 research questions is available. The data submitted by the company are therefore unusable.

No suitable data which would allow deriving an added benefit of risankizumab in comparison with the ACT are available for either research question of this benefit assessment.

Results

The company's dossier did not present any suitable data for assessing the added benefit of risankizumab versus the ACT for bDMARD-naive patients or bDMARD-experienced patients with active psoriatic arthritis. This results in no hint of added benefit of risankizumab in comparison with the ACT; an added benefit is therefore not proven.

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

Based on the results presented, the probability and extent of added benefit of the drug risankizumab in comparison with the ACT are assessed as follows:

Table 3 summarizes the probability and extent of added benefit of risankizumab.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Risankizumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with active psoriatic arthritis who have experienced inadequate response or intolerance to a prior DMARD therapy[b]	A TNF-alpha antagonist (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an interleukin inhibitor (ixekizumab or secukinumab or ustekinumab), if applicable in combination with methotrexate	Added benefit not proven
2	Adults with active psoriatic arthritis who have experienced inadequate response or intolerance to prior therapy with bDMARDs	Switch to another biologic disease-modifying antirheumatic drug (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab or ustekinumab), if applicable in combination with methotrexate	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. The patient population considered for research question 1 consists of bDMARD-naive patients.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

The approach for deriving an overall conclusion on 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 is to assess the added benefit of risankizumab, either as monotherapy or in combination with MTX, versus the ACT in adult patients with active psoriatic arthritis who have experienced inadequate response or intolerance to prior therapy with disease-modifying antirheumatic drugs (DMARDs).

The ACT specified by the G-BA depends on the patient's pretreatment. The resulting research questions are shown in Table 4.

Table 4: Research questions of the benefit assessment of risankizumab

Research question	Therapeutic indication	ACT[a]
1	Adults with active psoriatic arthritis who have experienced inadequate response or intolerance to prior DMARD therapy[b]	A TNF-alpha antagonist (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an interleukin inhibitor (ixekizumab or secukinumab or ustekinumab), if applicable in combination with methotrexate
2	Adults with active psoriatic arthritis who have experienced inadequate response or intolerance to prior therapy with bDMARDs	Switch to another biologic disease-modifying antirheumatic drug (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab or ustekinumab), if applicable in combination with methotrexate

a. Presented is the respective ACT specified by the G-BA.
b. The patient population analysed to answer research question 1 consists of bDMARD-naive patients.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

In the present assessment, the following designations are used for the patient populations of the 2 research questions:

- Research question 1: bDMARD-naive patients with active psoriatic arthritis who have experienced an inadequate response or intolerance to prior DMARD therapy
- Research question 2: patients with active psoriatic arthritis who have experienced an inadequate response or intolerance to prior bDMARD therapy

The company followed the G-BA's specification of the ACT. Overall, the company has drawn its conclusion on added benefit for the entire target population without asserting separate conclusions for the respective subpopulations for research questions 1 and 2. In line with the G-BA's specification, the present assessment attempted to answer the 2 research questions, each in comparison with the ACT specified by the G-BA. Since no usable data are available for either of the subpopulations designated by the G-BA, both research questions are assessed below in joint sections of the report (see Sections 2.3, 2.4, and 2.5).

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 deriving added benefit. This concurs with the company's inclusion criteria.

2.3 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 risankizumab (status: 29 September 2021)
- bibliographical literature search on risankizumab (last search on 20 September 2021)
- search in trial registries / trial results databases for studies on risankizumab (last search on 20 September 2021)
- search on the G-BA website for risankizumab (last search on 21 September 2021)

To check the completeness of the study pool:

- search in trial registries for studies on risankizumab (last search on 16 December 2021); for search strategies, see Appendix A of the full dossier assessment

The completeness check did not produce any relevant RCTs with risankizumab that were specifically conducted in the therapeutic indication of psoriatic arthritis. In its dossier, the company presented the RCTs UltlMMa-1 and UltlMMa-2, which investigated the therapeutic indication of plaque psoriasis. These studies included patients with plaque psoriasis with or without psoriatic arthritis.

UltlMMa-1 and UltlMMa-2 studies

The UltlMMa-1 and UltlMMa-2 studies are generally relevant for the present benefit assessment. However, the data submitted by the company are ultimately unsuitable for deriving a conclusion on added benefit because of missing data on the relevant subpopulations for research questions 1 and 2 of the present benefit assessment. Detailed reasons can be found in Section 2.3.2.

KEEPsAKE 1 and KEEPsAKE 2 studies

In its study pool, the company additionally lists the KEEPsAKE 1 [3] and KEEPsAKE 2 studies [4]. These 2 studies are placebo-controlled approval studies on risankizumab in the therapeutic indication of psoriatic arthritis. The company notes that it did not use the results of either study for deriving added benefit, because these studies do not allow a comparison with the ACT. Nevertheless, the company presented the results of these studies and used them as supplementary evidence in its derivation of added benefit.

The KEEPsAKE 1 and KEEPsAKE 2 studies are randomized, double-blind, placebo-controlled studies with risankizumab. They included adults with moderately to severely active psoriatic arthritis who had exhibited an inadequate response or intolerance to ≥ 1 nonbiological DMARD. In addition, ≤ 50% of the KEEPsAKE 2 population exhibited an inadequate response or intolerance to ≤ 2 bDMARDs.

Since both RCTs are placebo-controlled studies, the ACT has not been implemented and the studies are unsuitable for the present benefit assessment.

IMMvent and IMMerge studies

In its derivation of added benefit (Module 4 A, Section 4.4.2), the company has provided as supplementary evidence results from 2 additional studies in the therapeutic indication of plaque psoriasis with a psoriatic arthritis subpopulation. These are randomized, double-blind studies comparing risankizumab versus adalimumab (IMMvent study [5]) or secukinumab (IMMerge study [6]). The study populations each include adults with moderate to severe plaque psoriasis with or without psoriatic arthritis. According to the company, however, it was impossible to retrospectively determine whether these patients had active psoriatic arthritis because no classification according to CASPAR criteria had been carried out. In addition, the IMMvent study duration of 16 weeks was too short for a parallel comparison. In the company's opinion, it is impossible to adequately interpret the results of the IMMvent and IMMerge studies.

The company's rationale was found plausible. Additionally, the present assessment of added benefit of risankizumab requires results on indication-specific outcomes, which were not collected in either study. Overall, the IMMvent and IMMerge studies are unsuitable for assessing the added benefit of risankizumab in the therapeutic indication of psoriatic arthritis.

2.3.1 Studies included

The studies listed in the following Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: risankizumab vs. ustekinumab

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
M16-008 (UltIMMa-1[d])	Yes[e]	Yes	No	Yes [7]	Yes [8,9]	Yes [10,11]
M15-995 (UltIMMa-2[d])	Yes[e]	Yes	No	Yes [12]	Yes [13,14]	Yes [10,11]

a. Study for which the company was sponsor.
b. References of study registry entries and any available reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website.
d. In the tables below, the study is referred to by this acronym.
e. These studies were submitted by the company to obtain approval for risankizumab in the therapeutic indication of plaque psoriasis.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

2.3.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison: risankizumab vs. ustekinumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
UltIMMa-1	RCT, parallel, double-blind	▪ Adults (≥ 18 years) with moderate to severe plaque psoriasis (BSA ≥ 10%, PASI ≥ 12 and sPGA ≥ 3) ▪ with or without psoriatic arthritis[b] ▪ diagnosis of the disease at least 6 months before the 1st dose of the study medication ▪ candidates for systemic therapy or phototherapy ▪ candidates for ustekinumab[c] treatment	Risankizumab (N = 304) Ustekinumab (N = 100) Placebo (N = 102)[d] PsA subpopulation presented by the company[e,f] Risankizumab (n = 57) Ustekinumab (n = 11)	Screening: 1–6 weeks Treatment: 52 weeks[g] Follow-up: in Week 56[h]	79 centres in Australia, Canada, Czech Republic, Germany, France, Japan, South Korea, United States 02/2016–09/2017	Primary: PASI 90 at Week 16; sPGA of 0 or 1 at Week 16 Secondary: all-cause mortality, symptoms, health status, health-related quality of life, AEs
UltIMMa-2	RCT, parallel, double-blind	▪ Adults (≥ 18 years) with moderate to severe plaque psoriasis (BSA ≥ 10%, PASI ≥ 12 and sPGA ≥ 3) ▪ with or without psoriatic arthritis[b] ▪ diagnosis of the disease at least 6 months before the 1st dose of the study medication ▪ candidates for systemic therapy or phototherapy ▪ candidates for ustekinumab[c] treatment	Risankizumab (N = 294) Ustekinumab (N = 99) Placebo (N = 98)[d] PsA subpopulation presented by the company[e,f] Risankizumab (n = 37) Ustekinumab (n = 15)	Screening: 1–6 weeks Treatment: 52 weeks[g] Follow-up: in Week 56[h]	64 centres in Austria, Belgium, Canada, France, Germany, Mexico, Poland, Portugal, Spain, United States 03/2016–09/2017	Primary: PASI 90 at Week 16; sPGA of 0 or 1 at Week 16 Secondary: all-cause mortality, symptoms, health status, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, direct comparison: risankizumab vs. ustekinumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include data only the basis of the information provided by the company's Module 4 A.
b. Patients with a prior history of or suspected psoriatic arthritis were evaluated at selected study sites using CASPAR criteria.
c. In compliance with the local SPC.
d. This arm is irrelevant for the assessment and is not presented in the following tables.
e. According to the company, the subpopulation it formed comprises patients with active psoriatic arthritis as defined by CASPAR criteria. Due to missing information on prior treatment, the subpopulation may potentially include some treatment-naive patients.
f. In its table on study characteristics (Table 4-13 in Module 4 A), the company provides markedly discrepant information on the number of patients in the PsA subpopulation formed by the company: UltlMMa-1: 35 versus 8 patients; UltlMMa-2: 19 versus 6 patients (intervention versus control arm). The further characterization of the subpopulations is based on the above figures, however, which are therefore used for the present assessment.
g. Last dose of the study medication in Week 40.
h. After Week 52, patients had the option of participating in an open-label extension study (M15-997 study) (in which case there was no follow-up visit). Patients who did not participate in this extension study had their last follow-up visit in Week 56.

AE: adverse event; BSA: body surface area; CASPAR: Classification for Psoriatic Arthritis; n: relevant subpopulation; N: number of randomized patients; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis; RCT: randomized controlled trial; sPGA: static Physician Global Assessment; SPC: Summary of Product Characteristics

Table 7: Characteristics of the interventions – RCT, direct comparison: risankizumab vs. ustekinumab

Study	Intervention	Comparison
UltIMMa-1	Risankizumab 150 mg (2 x 75 mg) s.c. in Weeks 0, 4, 16, 28, and 40	Ustekinumab s.c. in Weeks 0, 4, 16, 28 and 40 based on body weight: ▪ ≤ 100 kg = 45 mg ▪ > 100 kg = 90 mg
	+ Ustekinumab placebo in Weeks 0, 4, 16, 28, and 40	+ Risankizumab placebo in Weeks 0, 4, 16, 28, and 40
	Prohibited prior and concomitant treatment ▪ Biologics: ▫ Ustekinumab, guselkumab, tildrakizumab ▫ Secukinumab: ≤ 6 months before randomization ▫ Brodalumab, ixekizumab: ≤ 4 months before randomization ▫ Adalimumab, infliximab, investigational drugs for the treatment of psoriasis: ≤ 12 weeks before randomization ▫ Etanercept: ≤ 6 weeks before randomization ▪ Live vaccines: ≤ 6 weeks before randomization ▪ Further experimental drugs, systemic immunomodulators (e.g. MTX, ciclosporin A, cyclophosphamide, tofacitinib, apremilast), other systemic psoriasis therapies (e.g. retinoids, fumarates), photochemotherapy (PUVA): ≤ 30 days before randomization ▪ Phototherapy (e.g. UVA, UVB): ≤ 14 days before randomization ▪ Topical skin treatment (e.g. corticosteroids[a], vitamin D analogues, pimecrolimus, retinoids, salicylic acid, salicyl vaseline, lactic acid, tacrolimus, tar, urea, anthralin, alpha-hydroxy acid, fruit acid): ≤ 14 days before randomization	
UltIMMa-2	See UltIMMa-1	

a. Mild topical corticosteroids (e.g. desonide) or low-potency corticosteroids (e.g. hydrocortisone 0.5–2.5%) may be used on the face, armpits, and/or in the genital area. Exception: within 24 hours prior to visits with PASI assessment.

MTX: methotrexate; PASI: Psoriasis Area and Severity Index; PUVA: psoralen and ultraviolet-A light; RCT: randomized controlled trial; s.c.: subcutaneous; UVA: ultraviolet A light; UVB: ultraviolet B light

For its benefit assessment, the company submitted the UltlMMa-1 and UltlMMa-2 studies. These studies had already been included in the first assessment of risankizumab in patients with plaque psoriasis (IQWiG assessment A19-41, Addendum A19-87) [15,16].

The UltIMMa-1 and UltIMMa-2 studies are randomized, double-blind, parallel-group studies with identical protocols (twin studies) conducted in 79 and 64 study sites worldwide. The studies compared risankizumab versus placebo and ustekinumab in adults with moderate to severe plaque psoriasis (≥ 10% body surface area [BSA] affected, PASI ≥ 12 and sPGA ≥ 3). While the presence of psoriatic arthritis was not a prerequisite for inclusion in the studies, patients who had psoriatic arthritis in addition to plaque psoriasis were eligible for inclusion. Patients with a prior history of or suspected psoriatic arthritis were evaluated according to CASPAR criteria at selected study sites, and further surveys were conducted if psoriatic arthritis was confirmed.

The UltIMMa-1 study included a total of 506 patients, and the UltIMMa- study, 491 patients. In each study, patients were randomly allocated in a 3:1:1 ratio to the study arms risankizumab (UltIMMa-1: N = 304; UltIMMa-2: N = 294), ustekinumab (UltIMMa-1: N = 100; UltIMMa-2: N = 99), and placebo (UltIMMa-1: N = 102; UltIMMa-: N = 98). Both studies were stratified by the factors of body weight (≤ 100 kg versus > 100 kg) and pretreatment with TNF antagonists (0 versus ≥ 1). The respective placebo arms are irrelevant for the assessment and are no longer considered hereinafter.

Both studies included patients whom the investigator deemed to be candidates for systemic therapy or phototherapy and who were candidates for treatment with ustekinumab in accordance with the local Summary of Product Characteristics (SPC) in the therapeutic indication of plaque psoriasis. Based on these specifications, treatment-naive patients were allowed to be included in the studies as well.

The design of both studies included a (1-week to 6-week) screening phase followed by a 52-week blinded treatment phase (last dose of study medication in Week 40). Subsequently, patients had the option of either ending their study participation or participating in an open-label extension study (M15-997 study). Patients who did not participate in this extension study had their last follow-up visit in Week 56. Patients who participated in the extension study had no follow-up visit. Irrespective of whether patients participated in the extension study, data were available for the time of treatment end after 52 weeks.

In both studies, treatment in the risankizumab and ustekinumab arms was in line with the regimen described in Table 7 and was largely in compliance with the respective SPC [17,18]. According to the risankizumab and ustekinumab SPCs, however, consideration should be given to discontinuing treatment in patients who show no response after 16 or 28 weeks of treatment, respectively. The company failed to address the latter recommendation in both the study documents and the dossier.

The primary outcomes of both studies were PASI 90 and an sPGA value of 0 or 1 at Week 16. Secondary outcomes were all-cause mortality, outcomes of the morbidity and health-related quality of life categories as well as AEs.

Relevant subpopulations of the UltlMMa1- and UltlMMa-2 studies

The relevant population for the present benefit assessment is UltlMMa-1 and UltlMMa-2 participants who simultaneously exhibit both moderate to severe plaque psoriasis and active psoriatic arthritis. In addition, patients had to have received prior treatment with at least 1 DMARD, with said treatment having been inadequate or not tolerated. For this relevant subpopulation, specific information on prior treatment received is additionally required to be able to draw separate conclusions for research question 1 (bDMARD-naive patients) and research question 2 (bDMARD-experienced patients).

No data available for the relevant subpopulations

From both studies, the company submitted analyses on the subpopulation of patients who have active psoriatic arthritis according to CASPAR criteria. The company did not further restrict this subpopulation to patients who had received prior treatment with at least 1 DMARD. Consequently, the subpopuluation formed by the company was not categorized by the same in terms of prior therapy received, thus providing no separate data for bDMARD-naive patients (research question 1) versus bDMARD-experienced patients (research question 2). The company justifies its approach by stating that any further adjustment (particularly breaking down patients by prior therapy) would lead to an additional reduction of the observed subpopulation, which in turn would further diminish the informative value of results.

The company's approach was not appropriate. In both studies, the inclusion criteria were not limited to patients who are candidates for risankizumab or ustekinumab therapy in the present therapeutic indication according to German approval. Therefore, the subpopulation formed by the company may potentially include some patients who have not had any prior DMARD therapy. Data on the percentage of patients without prior systemic therapy are available for the total populations of the UltlMMa-1 and UltlMMa-2 studies as well as the respective risankizumab and ustekinumab arms. It equals 32% in both studies (UltIMMa-1: 128 of 404 patients; UltIMMa-2: 124 of 393 patients) [19]. Module 4 A does not provide the percentage of patients treated off label in each of the UltlMMa-1 and UltlMMa-2 subpopulations formed by the company (see Appendix B of the full dossier assessment).

Furthermore, the company did not submit any separate analyses for the patient populations of bDMARD-naive patients (research question 1) or bDMARD-experienced patients (research question 2), which would be needed for the present benefit assessment to draw separate conclusions regarding the patient populations of research question 1 (bDMARD-naive patients) and research question 2 (bDMARD-experienced patients).

It is true that applying additional criteria or breaking down the subpopulations analysed by the company (UltMMa-1: N = 68; UltlMMa-2: N = 52) by the 2 research questions will likely reduce the size of the subpopulations. However, smaller subpopulation size alone is not a sufficient argument for analysing the 2 research questions jointly or for including patients with off-label prior treatment in the analysis.

Overall, the missing information on prior treatment renders the data presented by the company unusable. Given that the presented data cannot be used, a detailed investigation of further aspects was foregone (e.g. of the patient relevance of the presented outcomes, the availability of adequate ITT analyses and return rates as well as of suitable responder analyses taking into account the current General Methods [1]).

The company has presented no data for the risankizumab-methotrexate combination or for patients without concomitant moderate to severe plaque psoriasis.

No suitable data which would allow deriving an added benefit of risankizumab in comparison with the ACT are available for either research question of this benefit assessment.

2.4 Results on added benefit

The company's dossier did not present any suitable data for assessing the added benefit of risankizumab versus the ACT for bDMARD-naive patients or bDMARD-experienced patients with active psoriatic arthritis. This resulted in no hint of an added benefit of risankizumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 8 summarizes the result of the assessment of the added benefit of risankizumab in comparison with the ACT.

Table 8: Risankizumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with active psoriatic arthritis who have experienced an inadequate response or intolerance to prior DMARD therapy[b]	A TNF-alpha antagonist (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an interleukin inhibitor (ixekizumab or secukinumab or ustekinumab), if applicable in combination with methotrexate	Added benefit not proven
2	Adults with active psoriatic arthritis who have experienced inadequate response or intolerance to prior therapy with bDMARDs	Switch to another biologic disease-modifying antirheumatic drug (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab or ustekinumab), if applicable in combination with methotrexate	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. The patient population considered for research question 1 consists of bDMARD-naive patients.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

The assessment described above deviates from the assessment by the company, which derived an indication of a non-quantifiable added benefit for both research questions.

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

References for English extract

Please see full dossier assessment for full reference list.

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

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