IQWiG Reports – Commission No. A19-41

Risankizumab (plaque psoriasis) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Risankizumab (Plaque-Psoriasis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 August 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) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
2 May 2019

Internal Commission No.:
A19-41

Address of publisher:
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

Medical and scientific advice:

- Alexander Nast, Charité Universitätsmedizin, Berlin, Germany

IQWiG thanks the medical and scientific advisor for his 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.

IQWiG employees involved in the dossier assessment:

- Virginia Seiffart
- Lars Beckmann
- Judith Gibbert
- Florina Kerekes
- Ulrike Lampert
- Katrin Nink
- Volker Vervölgyi
- Carolin Weigel

Keywords: risankizumab, psoriasis, benefit assessment, NCT02684357, NCT02684370, NCT03255382

Table of contents

List of tables[2]

Page

[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
BSA	body surface area
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)
LOCF	last observation carried forward
MI	multiple imputation
NAPSI	Nail Psoriasis Severity Index
NB-UVB	narrowband ultraviolet B
NRI	non-responder imputation
PASI	Psoriasis Area and Severity Index
PPASI	Palmoplantar Psoriasis Area and Severity Index
PSS	Psoriasis Symptom Scale
PSSI	Psoriasis Scalp Severity Index
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
sPGA	static Physician Global Assessment
TNF	tumour necrosis factor
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug risankizumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 2 May 2019.

Research question

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

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

Table 2: Research questions of the benefit assessment of risankizumab

Research question	Subindication	ACT[a]
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
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**

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

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

- research question A: adult patients who are not candidates for conventional treatment in the framework of initial systemic therapy
- research question B: adult patients with inadequate response or intolerance to systemic therapy

For research question A, deviating from the G-BA, the company referred to adult patients with moderate to severe plaque psoriasis who are candidates for initial systemic therapy as relevant

population, thus also including patients who are candidates for systemic therapy with conventional drugs. Besides, based on the status of the ACT from 12 September 2018, it named adalimumab or ciclosporin or methotrexate or ixekizumab or phototherapy (narrowband ultraviolet B light [NB-UVB], photo-brine therapy) or secukinumab as comparator therapies. With reference to the last consultation at the G-BA on 12 April 2018, the company additionally cited fumaric acid esters as comparator therapy and also selected fumaric acid esters from these options. This approach was inadequate. Fumaric acid esters, methotrexate, ciclosporin and phototherapy (NB-UVB, photo-brine therapy) are no options of the ACT specified by the G-BA. The ACT additionally included the option of guselkumab, which was not mentioned by the company.

For research question B, the company chose ustekinumab from the options; this approach was adequate. Deviating from the specification of the ACT by the G-BA, the company did not mention guselkumab as a further option.

The population and the ACT specified by the G-BA were used for both research questions.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results for research question A: adult patients who are not candidates for conventional treatment in the framework of a first systemic therapy

The company presented results of the RCT M16-178 for research question A. The M16-178 study was an open-label, randomized study comparing risankizumab with fumaric acid esters in adults with moderate to severe plaque psoriasis. The included patients had to be naive to and candidates for systemic therapy. They also had to be candidates for treatment with fumaric acid esters, ciclosporin, methotrexate or phototherapy.

The data presented by the company were unsuitable to draw conclusions on the added benefit of risankizumab versus the ACT for the following reasons:

- Fumaric acid esters, the comparator intervention chosen by the company, was not an option of the ACT specified by the G-BA for research question A. As part of a reassessment of the generally accepted state of scientific knowledge, the G-BA informed the company of a change in the ACT on 12 September 2018. In accordance with this change and with the current specification of the ACT from 2 May 2019, fumaric acid esters were no longer an option of the ACT. The comparison of risankizumab versus fumaric acid esters is therefore not relevant for the present research question.
- As part of the adjustment of the ACT by the G-BA on 2 May 2019, the composition of the patient population for research question A has also changed. According to this adjustment, research question A only comprises patients who are not candidates for conventional treatment in the framework of a first systemic therapy. The M16-178 study explicitly

included patients who are candidates for a first systemic therapy with a conventional drug (e.g. fumaric acid esters, methotrexate or ciclosporin), however. Thus, the included patient population also does not concur with the patients eligible for research question A of the G-BA and is not relevant for the present research question.

However, the G-BA gave the company the opportunity to present the results of its M16-178 study on the direct comparison of risankizumab versus fumaric acid esters in the dossier as supplementary information to allow a discussion of the facts in the benefit assessment dossier and in the framework of the commenting procedure. The G-BA additionally commissioned IQWiG to assess and present the results of the M16-178 study in the framework of the benefit assessment as supplementary information. This presentation can be found in Appendix A of the full dossier assessment.

Results for research question B: adult patients with inadequate response or intolerance to systemic therapy

Following the company, the RCTs UltIMMa-1 and UltIMMa-2 were included for the assessment of the added benefit of risankizumab for the treatment of adult patients with inadequate response or intolerance to systemic therapy.

Study design

The studies UltIMMa-1 and UltIMMa-2 were randomized, double-blind, multicentre studies comparing risankizumab with ustekinumab and placebo.

The UltIMMa-1 study included a total of 506 patients, and the UltIMMa-2 study a total of 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), placebo (UltIMMa-1: N = 102; UltIMMa-2: N = 98) and ustekinumab (UltIMMa-1: N = 100; UltIMMa-2: N = 99). Stratification in both studies was by body weight (≤ 100 kg versus > 100 kg) and pretreatment with tumour necrosis factor (TNF) antagonists (0 versus ≥ 1).

Both studies included patients who, in the investigator's opinion, were candidates for systemic therapy or phototherapy and for whom treatment with ustekinumab was suitable in accordance with the local Summary of Product Characteristics (SPC). Hence, the inclusion criteria in both studies were not restricted to patients of the present research question B, i.e. those with inadequate response or intolerance to systemic therapy. The company therefore presented the results of a subpopulation. For both studies, the subpopulation used to answer research question B of the present benefit assessment corresponds to about one third of the patients originally randomized to the study arms. It comprised n = 100 (UltIMMa-1) and n = 90 (UltIMMa-2) patients in the risankizumab arm, and n = 34 (UltIMMa-1) and n = 36 (UltIMMa-2) patients in the ustekinumab arm.

In both studies, disease severity was defined using the following criteria: body surface area (BSA) ≥ 10%, Psoriasis Area and Severity Index (PASI) ≥ 12, and static Physician Global Assessment (sPGA) ≥ 3.

The design of both studies included a screening phase (1 to 6 weeks) followed by a 52-week blinded treatment phase (last dose of study medication in week 40).

In both studies, treatment with risankizumab and ustekinumab was largely in line with the corresponding SPCs.

Primary outcomes of both studies were PASI 90 and an sPGA score of 0 or 1 at week 16. Patient-relevant secondary outcomes were all-cause mortality, remission (PASI 100), outcomes on symptoms, health-related quality of life and side effects. The meta-analyses at week 52 were used for the benefit assessment.

Risk of bias and overall assessment of the certainty of conclusions

The risk of bias across outcomes was rated as low for both studies.

The risk of bias was rated as low for all-cause mortality and the outcomes on side effects (serious adverse events [SAEs], discontinuation due to adverse events [AEs] and infections and infestations). Proof, e.g. of an added benefit, can therefore be derived from the meta-analysis of the studies UltIMMa-1 and UltIMMa-2. There was a high risk of bias for all other outcomes, resulting in a reduced certainty of conclusions (at most indications). This can be addressed by appropriate sensitivity analyses, however, and may be upgraded to proof in the case of robust statistically significant results.

Results

Mortality

- All-cause mortality

No deaths occurred in the studies UltIMMa-1 and UltIMMa-2 until week 52. There was no hint of an added benefit of risankizumab in comparison with ustekinumab for all-cause mortality; an added benefit is therefore not proven.

Morbidity

- Remission (PASI 100)

The meta-analysis of the studies showed a statistically significant effect in favour of risankizumab for the outcome “remission” determined with the PASI 100.

Due to the high and differing proportions of imputed values, the results had a high risk of bias, however. For this reason, the results of sensitivity analyses (last observation carried forward [LOCF] and multiple imputation [MI]) were additionally considered for the responder analyses at week 52. The results of these analyses were of comparable magnitude and still showed a

statistically significant difference in favour of risankizumab. The result was therefore robust, so that a high certainty of results was assumed despite the outcome-specific high risk of bias.

Hence, there was proof of added benefit of risankizumab versus ustekinumab for the outcome "remission".

- Patient-reported absence of symptoms (outcomes "PSS itching", "PSS pain" and "PSS burning")

The meta-analysis showed a statistically significant effect in favour of risankizumab for each of the outcomes "Psoriasis Symptom Scale (PSS) itching", "PSS pain" and "PSS burning". However, there was an effect modification by the characteristic "age" for all 3 outcomes. As a result, there was no hint of an added benefit of risankizumab in comparison with ustekinumab for patients under the age of 40 years and for patients aged 65 years and older; an added benefit is therefore not proven. Under consideration of the high risk of bias, there was an indication of an added benefit of risankizumab in comparison with ustekinumab for each of these outcomes for patients aged between 40 and 64 years.

- Patient-reported absence of symptoms (PSS redness)

The meta-analysis showed a statistically significant effect in favour of risankizumab for the outcome "PSS redness". However, there was an effect modification by the characteristic "previous biologic treatment". As a result, there was no hint of an added benefit of risankizumab in comparison with ustekinumab for patients without previous biologic treatment; an added benefit is therefore not proven. Under consideration of the high risk of bias, there was an indication of an added benefit of risankizumab in comparison with ustekinumab for this outcome for patients pretreated with biologics.

- Further patient-reported symptoms (particularly scaling, cracking and bleeding)

The company's dossier contained no data for further outcomes of patient-reported symptoms (particularly scaling, cracking and bleeding).

- Absence of symptoms on hands and feet (Palmoplantar Psoriasis Area and Severity Index [PPASI] 0)

There were no usable data for the outcome "absence of symptoms on hands and feet (PPASI 0)". For its analyses, the company used the subpopulation of patients with palmoplantar psoriasis (PPASI > 0) at baseline. These analyses did not consider an important proportion of the randomized patients and were therefore unsuitable for the derivation of the added benefit.

There was no hint of an added benefit of risankizumab in comparison with ustekinumab for the outcome "absence of symptoms on hands and feet (PPASI 0)"; an added benefit is therefore not proven.

- Absence of symptoms on the scalp (Psoriasis Scalp Severity Index [PSSI] 0)

The meta-analysis of the studies showed a statistically significant difference in favour of risankizumab for the outcome "absence of symptoms on the scalp (PSSI 0)". Under consideration of the high risk of bias, there was an indication of an added benefit of risankizumab in comparison with ustekinumab for this outcome.

- Absence of symptoms on fingernails (Nail Psoriasis Severity Index [NAPSI]-finger 0)

There were no usable data for the outcome "absence of symptoms on fingernails (NAPSI-finger 0)". For its analyses, the company used the subpopulation of patients with nail psoriasis (NAPSI-finger > 0) at baseline. These analyses did not consider an important proportion of the randomized patients and were therefore unsuitable for the derivation of the added benefit.

There was no hint of an added benefit of risankizumab in comparison with ustekinumab for the outcome "absence of symptoms on fingernails (NAPSI-finger 0)"; an added benefit is therefore not proven.

- Health status (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS])

A statistically significant difference in favour of risankizumab was shown for the outcome "health status" measured with the EQ-5D VAS. In addition, there was an effect modification by the characteristic "sex" for this outcome. As a result, there was no hint of an added benefit of risankizumab in comparison with ustekinumab for women; an added benefit for women is therefore not proven. Under consideration of the high risk of bias, there was an indication of an added benefit of risankizumab in comparison with ustekinumab for this outcome for men.

Health-related quality of life

- Dermatology Life Quality Index (DLQI) (0 or 1)

The meta-analysis of the studies showed a statistically significant difference in favour of risankizumab for the outcome "health-related quality of life" measured with the DLQI. Under consideration of the high risk of bias, there was an indication of an added benefit of risankizumab in comparison with ustekinumab for this outcome.

Side effects

- Serious adverse events, discontinuation due to adverse events, and infections and infestations

The meta-analysis of the studies showed no statistically significant differences between the treatment groups for the outcomes "SAEs", "discontinuation due to AEs", and "infections and infestations". Consequently, for the outcomes "SAEs", "discontinuation due to AEs", and "infections and infestations", there was no hint of greater or lesser harm from risankizumab in comparison with ustekinumab; greater or lesser harm is therefore not proven.

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

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

Research question A: adult patients who are not candidates for conventional treatment in the framework of initial systemic therapy

Since the company presented no relevant data for the assessment of the added benefit of risankizumab in comparison with the ACT in adult patients who are not candidates for conventional treatment in the framework of initial systemic therapy, an added benefit of risankizumab is not proven for these patients.

Research question B: adult patients with inadequate response or intolerance to systemic therapy

In the overall assessment, there are only positive effects – partly only in subgroups – with different certainty of results (proof or indication) for risankizumab in comparison with ustekinumab in the outcome categories of morbidity and health-related quality of life. The extent ranges from considerable to minor or non-quantifiable. There is proof of considerable added benefit for remission (PASI 100).

In summary, there is therefore proof of considerable added benefit of risankizumab in comparison with ustekinumab for adult patients with moderate to severe plaque psoriasis with inadequate response or intolerance to systemic therapy.

Table 3 shows a summary of probability and extent of the 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	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 approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

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

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

Table 4: Research questions of the benefit assessment of risankizumab

Research question	Subindication	ACT[a]
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
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**

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 specified the ACTs listed in Table 4 (status: May 2019) at the same time as the company submitted the dossier. Deviating from the G-BA's specification, the company in its

dossier investigated research questions A and B for the populations and comparator therapies presented below:

- Research question A:
  - Adult patients with moderate to severe plaque psoriasis who are candidates for initial systemic therapy
  - Comparator therapy (based on the status from 12 September 2018): adalimumab or ciclosporin or ixekizumab or methotrexate or phototherapy ([NB-UVB, photo-brine therapy) or secukinumab. With reference to the final dossier consultation on 12 April 2018, the company additionally cited fumaric acid esters as comparator therapy and also selected fumaric acid esters from these options.
- Research question B:
  - Adult patients with moderate to severe plaque psoriasis with inadequate response to systemic therapy
  - Comparator therapy: adalimumab or infliximab or ixekizumab or secukinumab or ustekinumab. The company chose ustekinumab from the options.

Deviating from the company, both the patient population and the ACT specified by the G-BA were taken into account for the present research question A as shown in Table 4 [3]. Fumaric acid esters, methotrexate, ciclosporin and phototherapy (NB-UVB, photo-brine therapy) were no longer options of the ACT specified by the G-BA. The ACT additionally included the option of guselkumab, which was not mentioned by the company. The G-BA's specification for fumaric acid esters was based on a reassessment of the general state of scientific knowledge (see Section 2.3 and Section 2.6.1 of the full dossier assessment). The G-BA informed the company of this on 12 September 2018. The new adjustment of the ACT by the G-BA on 2 May 2019 also entailed an adjustment of the composition of the patient population. According to this adjustment, research question A only comprises patients who are not candidates for conventional treatment in the framework of a first systemic therapy. In its research question, the company investigated a broader patient population consisting of patients who are candidate for initial systemic therapy (see Section 2.3 and Section 2.6.2 of the full dossier assessment).

However, the G-BA gave the company the opportunity to present the results of its M16-178 study on the direct comparison of risankizumab versus fumaric acid esters in the dossier as supplementary information to allow a discussion of the facts in the benefit assessment dossier and in the framework of the commenting procedure. The G-BA additionally commissioned IQWiG to assess and present the results of the M16-178 study in the framework of the benefit assessment as supplementary information (see Appendix A of the full dossier assessment).

For research question B, the company chose ustekinumab from the options; this approach was adequate. Deviating from the specification of the ACT by the G-BA, the company did not mention guselkumab as a further option. In addition, the description of the patient population

did not include the addition “or intolerance”. Both the patient population and the ACT specified by the G-BA were also used for research question B (see Sections 2.6.1 and 2.6.2 of the full dossier assessment).

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

- research question A: adult patients who are not candidates for conventional treatment in the framework of initial systemic therapy
- research question B: adult patients with inadequate response or intolerance to systemic therapy

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company’s inclusion criteria.

2.3 Research question A: adult patients who are not candidates for conventional treatment in the framework of initial systemic therapy

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on risankizumab (status: 15 March 2019)
- bibliographical literature search on risankizumab (last search on 15 February 2019)
- search in trial registries for studies on risankizumab (last search on 15 February 2019)

To check the completeness of the study pool:

- search in trial registries for studies on risankizumab (last search on 16 May 2019)

No relevant study was identified from the check.

Study pool of the company

From the steps of information retrieval mentioned, the company identified the RCT M16-178 [4-9], which it considered relevant for the benefit assessment and used for the derivation of the added benefit, for its research question A.

The M16-178 study was an open-label, randomized study comparing risankizumab with fumaric acid esters in adults with moderate to severe plaque psoriasis. The included patients had to be naive to and candidates for systemic therapy. They also had to be candidates for treatment with fumaric acid esters, ciclosporin, methotrexate or phototherapy. The design of

the study and the characteristics of the interventions are presented in Appendix A.1 (Table 24 and Table 25) of the full dossier assessment.

The data presented by the company were unsuitable to draw conclusions on the added benefit of risankizumab versus the ACT for the following reasons:

- Fumaric acid esters, the comparator intervention chosen by the company, was not an option of the ACT specified by the G-BA for research question A (see Section 2.2). As part of a reassessment of the generally accepted state of scientific knowledge, the G-BA informed the company of a change in the ACT on 12 September 2018. In accordance with this change and with the current specification of the ACT from 2 May 2019, fumaric acid esters were no longer an option of the ACT. The comparison of risankizumab versus fumaric acid esters is therefore not relevant for the present research question.
- As part of the adjustment of the ACT by the G-BA on 2 May 2019, the composition of the patient population for research question A has also changed. According to this adjustment, research question A only comprises patients who are not candidates for conventional treatment in the framework of a first systemic therapy. The M16-178 study explicitly included patients who are candidates for a first systemic therapy with a conventional drug (e.g. fumaric acid esters, methotrexate or ciclosporin), however. Thus, the included patient population also does not concur with the patients eligible for research question A of the G-BA and is not relevant for the present research question.

As described in Section 2.2, the G-BA commissioned IQWiG to analyse and present the results of the M16-178 study of direct comparison as part of the benefit assessment. The corresponding presentation can be found in Appendix A of the full dossier assessment.

2.3.2 Results on added benefit

The company presented no relevant data for the assessment of the added benefit of risankizumab in comparison with the ACT in adult patients who are not candidates for conventional treatment in the framework of a first systemic therapy. This resulted in no hint of an added benefit of risankizumab in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

Since the company presented no relevant data for the assessment of the added benefit of risankizumab in comparison with the ACT in adult patients who are not candidates for conventional treatment in the framework of initial systemic therapy, an added benefit of risankizumab is not proven for these patients.

This assessment deviates from that of the company, which overall derived an indication of considerable added benefit for the company’s research question A on the basis of the data presented.

2.3.4 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

2.4 Research question B: adult patients with inadequate response or intolerance to systemic therapy

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on risankizumab (status: 15 March 2019)
- bibliographical literature search on risankizumab (last search on 15 February 2019)
- search in trial registries for studies on risankizumab (last search on 15 February 2019)

To check the completeness of the study pool:

- search in trial registries for studies on risankizumab (last search on 16 May 2019)

The check identified no additional relevant study.

2.4.1.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: risankizumab vs. ustekinumab (research question B)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
M16-008 (UltIMMa-1[b])	Yes	Yes	No
M15-995 (UltIMMa-2[b])	Yes	Yes	No
a: Study sponsored by the company. b: In the following tables, the study is referred to with this abbreviated form. RCT: randomized controlled trial; vs.: versus			

Section 2.3.4 contains a reference list for the studies included.

2.4.1.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison: risankizumab vs. ustekinumab (research question B)

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) ▪ diagnosis of the disease at least 6 months before the first dose of the study medication ▪ candidates for systemic therapy or phototherapy ▪ candidates for treatment with ustekinumab[b]	Risankizumab (N = 304) ustekinumab (N = 100) placebo (N = 102)[c] Relevant subpopulation thereof[d]: risankizumab (n = 100) ustekinumab (n = 34)	Screening: 1–6 weeks Treatment duration: 52 weeks[e] Follow-up: in week 56[f]	79 centres in Australia, Canada, Czech Republic, Germany, France, Japan, South Korea, USA 2/2016–9/2017	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) ▪ diagnosis of the disease at least 6 months before the first dose of the study medication ▪ candidates for systemic therapy or phototherapy ▪ candidates for treatment with ustekinumab[b]	Risankizumab (N = 294) ustekinumab (N = 99) placebo (N = 98)[c] Relevant subpopulation thereof[d]: risankizumab (n = 90) ustekinumab (n = 36)	Screening: 1–6 weeks Treatment duration: 52 weeks[e] Follow-up: in week 56[f]	64 centres in Austria, Belgium, Canada, France, Germany, Mexico, Poland, Portugal, Spain, USA 3/2016–9/2017	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

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison: risankizumab vs. ustekinumab (research question B) (continued)

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b: In compliance with the local SPC.
c: The arm is not relevant for the assessment and is no longer presented in the following tables.
d: According to the company in Module 4 A, the subpopulation comprises patients who have not responded to other systemic therapies or who had contraindications or intolerance to those therapies (details on the composition of the subpopulation can be found in Section 2.4.1.2 of the present assessment).
e: Last dose of the study medication in week 40.
f: After week 52, the patients hat the opportunity to participate in an open-label extension study (study M15-997) (these patients had 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; n: relevant subpopulation; N: number of randomized patients; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; sPGA: static Physician Global Assessment; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: risankizumab vs. ustekinumab (research question B)

Study	Intervention	Comparison
UltIMMa-1	Risankizumab 150 mg (2 x 75 mg) SC in weeks 0, 4, 16, 28 and 40	Weight-dependent ustekinumab SC in weeks 0, 4, 16, 28 and 40: ▪ ≤ 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 investigational drugs, systemic immunomodulators (e.g. MTX, ciclosporin A, cyclophosphamide, tofacitinib, apremilast), other systemic treatments for psoriasis (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, salicylic vaseline, lactic acid, tacrolimus, tar, urea, anthralin, alpha hydroxy acid, fruit acid): ≤ 14 days before randomization	
UltIMMa-2	See UltIMMa-1	

a: Topical corticosteroids of US class 7 (mild, e.g. desonide) or of German class 1 (least potent, e.g. hydrocortisone 0.5–2.5%) are permitted for use on the face, axilla, and/or genitalia. Exception: Within 24 hours prior to visits requiring PASI assessment.

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

Description of the study design

The studies UltIMMa-1 and UltIMMa-2 were randomized, double-blind, parallel-group studies with identical protocols (twin studies) conducted in 79 and 64 study centres worldwide. The studies investigated risankizumab in comparison with placebo and ustekinumab in adults with moderate to severe plaque psoriasis. In both studies, disease severity was defined using the following criteria: BSA ≥ 10%, PASI ≥ 12, and sPGA ≥ 3. For the present benefit assessment, this definition of the severity grade was rated as adequate representation of moderate to severe psoriasis (see Section 2.6.4.1 of the full dossier assessment).

The UltIMMa-1 study included a total of 506 patients, and the UltIMMa-2 study a total of 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), placebo (UltIMMa-1: N = 102;

UltIMMa-2: N = 98) and ustekinumab (UltIMMa-1: N = 100; UltIMMa-2: N = 99). Stratification in both studies was by the factors body weight (≤ 100 kg versus > 100 kg) and pretreatment with TNF antagonists (0 versus ≥ 1). The respective placebo arms are not relevant for the assessment and are no longer considered hereinafter.

Both studies included patients who, in the investigator's opinion, were candidates for systemic therapy or phototherapy and for whom treatment with ustekinumab was suitable in accordance with the local SPC. Hence, the inclusion criteria in both studies were not restricted to patients of the present research question B, i.e. those with inadequate response or intolerance to systemic therapy. The company therefore presented the results of a subpopulation (see below).

The design of both studies included a screening phase (1 to 6 weeks) followed by a 52-week blinded treatment phase (last dose of study medication in week 40). Patients could then either end their participation in the study or participate in an open-label extension study (study M15-997). 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, did not have a follow-up visit. Irrespective of whether the patients participated in the extension study, there were data available on the end of treatment after 52 weeks, on which the present assessment was based.

Treatment in both studies, both in the risankizumab and in the ustekinumab arm, was conducted according to the regimen described in Table 7 and was largely in compliance with the respective SPC [10,11]. According to the SPCs of risankizumab and ustekinumab, however, consideration should be given to discontinuing treatment in patients who have shown no response after 16 or 28 weeks of treatment respectively. The latter was not addressed by the company in the study documents or in the dossier. It is assumed, however, that this deviation had no relevant influence on the study results.

Primary outcomes of both studies were PASI 90 and an sPGA score of 0 or 1 at week 16. Patient-relevant secondary outcomes were all-cause mortality, remission (PASI 100), outcomes on symptoms, health-related quality of life and side effects.

Subpopulation relevant for the benefit assessment

The inclusion criteria in both studies were not restricted to patients of the present research question B, i.e. those with inadequate response or intolerance to systemic therapy.

In the description of the study design of the UltIMMa studies in Module 4 B, the company stated that it formed a corresponding subpopulation for research question B. It referred to the different national approvals of ustekinumab and only included those patients who are candidates for treatment with ustekinumab according to the German approval (a detailed explanation can be found in Section 2.6.4.1 of the full dossier assessment). The company's approach was followed under the assumption that the local approvals of ustekinumab were consistently adhered to at inclusion.

Despite this approach, the subpopulation formed by the company also included patients without prior systemic therapy (UltIMMa-1: n = 15; UltIMMa-2: n = 13) and therefore cannot be allocated to the present research question B. However, the proportion of these treatment-naive patients (10.8%) accounted for less than 20% of the subpopulation and did not call the transferability of the results into question. The subpopulation formed by the company can thus be used for the present benefit assessment.

For both studies, the subpopulation used to answer research question B corresponds to about one third of the patients originally randomized to the study arms. It comprised n = 100 (UltIMMa-1) and n = 90 (UltIMMa-2) patients in the risankizumab arm, and n = 34 (UltIMMa-1) and n = 36 (UltIMMa-2) patients in the ustekinumab arm.

Table 8 shows the characteristics of the patients in the studies included.

Table 8: Characteristics of the subpopulations – RCT, direct comparison: risankizumab vs. ustekinumab (research question B)

Study Characteristics Category	UltIMMa-1		UltIMMa-2	
	Risankizumab	Ustekinumab	Risankizumab	Ustekinumab
	N[a] = 100	N[a] = 34	N[a] = 90	N[a] = 36
Age [years], mean (SD)	50 (12)	47 (14)	45 (12)	47 (14)
Sex [F/M], %	28/72	26/74	36/64	31/69
Body weight, n (%)				
≤ 100 kg	81 (81.0)	28 (82.4)	67 (74.4)	27 (75.0)
> 100 kg	19 (19.0)	6 (17.6)	23 (25.6)	9 (25.0)
Ethnicity, n (%)				
White	62 (62.0)	21 (61.8)	83 (92.2)	35 (97.2)
Non-white	38 (38.0)	13 (38.2)	7 (7.8)	1 (2.8)
Geographical region, n (%)				
USA	26 (26.0)	7 (20.6)	19 (21.1)	9 (25.0)
Asia	31 (31.0)	10 (29.4)	–	–
Other	43 (43.0)	17 (50.0)	71 (78.9)	27 (75.0)
Duration of disease [years], mean (SD)	19.2 (12.2)	16.6 (9.5)	20.6 (11.2)	21.7 (12.6)
Known PsA (diagnosed or suspected), n (%)	35 (35.0)	7 (20.6)	24 (26.7)	8 (22.2)
Nail psoriasis (NAPSI > 0), n (%)	68 (68.0)	25 (73.5)	50 (55.6)	22 (61.1)
Palmoplantar psoriasis (PPASI > 0), n (%)	36 (36.0)	11 (32.4)	32 (35.6)	13 (36.1)
Psoriasis of scalp (PSSI > 0), n (%)	91 (91.0)	29 (85.3)	80 (88.9)	28 (77.8)
Psoriasis of face and neck, n (%)	ND	ND	ND	ND
Genital psoriasis, n (%)	ND	ND	ND	ND
sPGA, n (%)				
Moderate (3)	80 (80.0)	27 (79.4)	69 (76.7)	32 (88.9)
Severe (4)	20 (20.0)	7 (20.6)	21 (23.3)	4 (11.1)
PASI, mean (SD)	22.5 (9.1)	21.9 (8.1)	21.5 (7.8)	18.4 (6.9)
PASI ≥ 20, n (%)	ND[b]	ND[b]	ND[b]	ND[b]
DLQI, mean (SD)	12.2 (6.6)	12.6 (7.0)	13.7 (7.7)	11.5 (6.3)
DLQI > 10, n (%)	58 (58.0)	20 (58.8)	56 (62.2)	19 (52.8)
Pretreatment, n (%)[c]				
Topical therapy	30 (30.0)	12 (35.3)	8 (8.9)	3 (8.3)
Phototherapy/photochemotherapy	55 (55.0)	17 (50.0)	41 (45.6)	20 (55.6)
Non-biological systemic therapy	63 (63.0)	20 (58.8)	63 (70.0)	26 (72.2)
Biological therapy	51 (51.0)	15 (44.1)	47 (52.2)	16 (44.4)
TNF antagonist	39 (39.0)	15 (44.1)	36 (40.0)	11 (30.6)
Naive to systemic therapy, n (%)	10 (10.0)	5 (14.7)	11 (12.2)	2 (5.6)

(continued)

Table 8: Characteristics of the subpopulations – RCT, direct comparison: risankizumab vs. ustekinumab (research question B) (continued)

Study Characteristics Category	UltIMMa-1		UltIMMa-2	
	Risankizumab	Ustekinumab	Risankizumab	Ustekinumab
	N[a] = 100	N[a] = 34	N[a] = 90	N[a] = 36
Treatment discontinuation, n (%)	3 (3.0)[d]	2 (5.9)[d]	1 (1.1)[d]	5 (11.7)[d]
Study discontinuation, n (%)	2 (2.0[d])	3 (8.8[d])	2 (2.2[d])	4 (11.1[d])

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant
b: Proportion of patients with PASI ≥ 19.4 (median of the pooled populations of UltIMMa-1 and UltIMMa-2 at baseline): 54 (54.0%) vs. 17 (50.0%) in the risankizumab and ustekinumab arm of UltIMMa-1 study, and 49 (54.4%) vs. 11 (30.6%) in the risankizumab and ustekinumab arm of the UltIMMa-2 study.
c: Multiple answers possible.
d: Institute's calculation
DLQI: Dermatology Life Quality Index; F: female; M: male; n: number of patients in the category; N: number of randomized patients; NAPSI: Nail Psoriasis Severity Index; ND: no data; PASI: Psoriasis Area and Severity Index; PPASI: Palmoplantar Psoriasis Area and Severity Index; PsA: psoriatic arthritis; PSSI: Psoriasis Scalp Severity Index; RCT: randomized controlled trial; SD: standard deviation; sPGA: static Physician Global Assessment; TNF: tumour necrosis factor; vs.: versus

The patient characteristics of the subpopulations were largely comparable both between the studies and between the treatment arms. The mean age of the participants in both studies was about 47 years; most of them were male and white. Regarding disease characteristics, there were differences in the proportions of patients with known psoriatic arthritis. Their proportion was higher in the risankizumab arm of the UltIMMa-1 study than in the ustekinumab arm. Both studies included patients with nail psoriasis at baseline, with the mean proportion being higher in the UltIMMa-1 study than in the UltIMMa-2 study. There were slight imbalances regarding pretreatment both between the studies and between the respective study arms. The UltIMMa-1 study included more patients with prior topical therapy (UltIMMa-1: about 33% versus UltIMMa-2: about 9%). An average of about 60% of the patients in the UltIMMa-1 study and of about 70% in the UltIMMa-2 study received non-biological systemic therapy.

With regard to the number of treatment and study discontinuations, the proportions in the risankizumab arms in both studies were about 2%, in the ustekinumab arms 6 to 9% in the UltIMMa-1 study and about 11% in the UltIMMa-2 study.

In summary, the demographic and clinical characteristics of the patients in these subpopulations were largely balanced both between the individual study arms and between the studies despite the imbalances mentioned.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: risankizumab vs. ustekinumab (research question B)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
UltIMMa-1	Yes	Yes	Yes	Yes	Yes	Yes	Low
UltIMMa-2	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for both studies. This concurs with the company's assessment.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.4.3.2 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - remission (PASI 100)
  - patient-reported absence of symptoms
    - itching (PSS itching 0)
    - pain (PSS pain 0)
    - redness (PSS redness 0)
    - burning (PSS burning 0)
  - further patient-reported symptoms (particularly scaling, cracking, bleeding)
  - absence of symptoms on the scalp (PSSI 0)
  - absence of symptoms on the nails (NAPSI 0)
  - absence of symptoms on hands and feet (PPASI 0)
  - health status (EQ-5D VAS)
- Health-related quality of life

- DLQI (0 or 1)

- Side effects
  - SAEs
  - discontinuation due to AEs
  - infections and infestations (System Organ Class [SOC])
  - if applicable, further specific AEs

Results at week 52 were used for the benefit assessment. The choice of patient-relevant outcomes deviates from that of the company, which considered further outcomes in the dossier (Module 4 B) (see Section 2.6.4.3.2 of the full dossier assessment).

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

Table 10: Matrix of outcomes – RCT, direct comparison: risankizumab vs. ustekinumab (research question B)

Study	Outcomes														
	All-cause mortality	**Remission (PASI 100)[a]**	**Itching (PSS itching 0)**	**Pain (PSS pain 0)**	**Redness (PSS redness 0)**	**Burning (PSS burning 0)**	**Further patient-reported symptoms (particularly scaling, cracking, bleeding)**	**Absence of symptoms on the scalp (PSSI 0)**	**Absence of symptoms on fingernails (NAPSI-finger 0)**	**Absence of symptoms on hands and feet (PPASI 0)**	**Health status (EQ-5D VAS)**	**Health-related quality of life (DLQI 0 or 1)**	**SAEs**	**Discontinuation due to AEs**	**Infections and infestations (SOC, AE)**
UltIMMa-1	Yes	Yes	Yes	Yes	Yes	Yes	No[b]	Yes	No[c, d]	No[c]	Yes	Yes	Yes	Yes	Yes
UltIMMa-2	Yes	Yes	Yes	Yes	Yes	Yes	No[b]	Yes	No[c, d]	No[c]	Yes	Yes	Yes	Yes	Yes

a: Improvement in score by 100% compared with baseline.
b: No data available; for reasons, see Section 2.6.4.3.2 of the full dossier assessment.
c: No usable data available; for reasons, see Section 2.6.4.3.2 of the full dossier assessment.
d: The results for patients with nail psoriasis at baseline are presented as supplementary information (see Table 13).

AE: adverse event; DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life-5 Dimensions; NAPSI: Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index; PPASI: Palmoplantar Psoriasis Area and Severity Index; PSS: Psoriasis Symptom Scale; PSSI: Psoriasis Scalp Severity Index;
RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.4.2.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: risankizumab vs. ustekinumab (research question B)

Study		Outcomes														
	Study level	All-cause mortality	Remission (PASI 100)[a]	Itching (PSS itching 0)	Pain (PSS pain 0)	Redness (PSS redness 0)	Burning (PSS burning 0)	Further patient-reported symptoms (particularly scaling, cracking, bleeding)	Absence of symptoms on the scalp (PSSI 0)	Absence of symptoms on fingernails (NAPSI-finger 0)	Absence of symptoms on hands and feet (PPASI 0)	Health status (EQ-5D VAS)	Health-related quality of life (DLQI 0 or 1)	SAEs	Discontinuation due to AEs	Infections and infestations (SOC, AE)
UltIMMa-1	L	L	H[b]	H[b]	H[b]	H[b]	H[b]	-[c]	H[d]	–[e]	–[e]	H[f]	H[f]	L	L	L
UltIMMa-2	L	L	H[b]	H[b]	H[b]	H[b]	H[b]	-[c]	H[b, d]	–[e]	–[e]	H[f]	H[f]	L	L	L

a: Improvement in score by 100% compared with baseline.
b: High and differential proportions of patients imputed using NRI (see Section 2.6.4.2 and Table 20 of the full dossier assessment)
c: No data available; for reasons, see Section 2.6.4.3.2 of the full dossier assessment.
d: The analysis includes only patients with PSSI > 0 at baseline. There are large and differential proportions of missing patients (risankizumab vs. ustekinumab: UltIMMa-1 9% vs. 14.7%; UltIMMa-2 11.1% vs. 22.2%).
e: No usable data available; for reasons, see Section 2.6.4.3.2 of the full dossier assessment.
f: Differential proportions of patients with missing values at week 52 (see Section 2.6.4.2 and Table 20 of the full dossier assessment).

AE: adverse event; DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; NAPSI: Nail Psoriasis Severity Index; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PPASI: Palmoplantar Psoriasis Area and Severity Index; PSS: Psoriasis Symptom Scale; PSSI: Psoriasis Scalp Severity Index; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The risk of bias was rated as high for the results on all outcomes except the outcome “all-cause mortality” and the outcomes on side effects (SAEs, discontinuation due to AEs, and infections and infestations). This deviates from the assessment of the company insofar as the company assessed the risk of bias as low for the results on all outcomes of both studies.

The high risk of bias for the outcomes of patient-reported absence of symptoms (PSS itching 0, PSS pain 0, PSS redness 0 and PSS burning 0) and of remission (PASI 100) in both studies, as

well as of the absence of symptoms on the scalp (PSSI 0) in the UltIMMa-2 study was due to the high and differential proportion of patients imputed using non-responder imputation (NRI). The high risk of bias for the outcome "absence of symptoms on the scalp" in the UltIMMa-1 and additionally in the UltIMMa-2 study was due to the high and differential proportion of missing patients. The high risk of bias for the outcome "health status", measured with the EQ-5D VAS, and for health-related quality of life, measured with the DLQI, in both studies was due to the differential proportions of patients with missing values at week 52. There were no data for outcomes on further patient-reported symptoms (particularly scaling, cracking and bleeding). There were no usable data for the outcomes "absence of symptoms on hands and feet (PPASI 0)" and "absence of symptoms on fingernails (NAPSI-finger 0)". Detailed comments on the risk of bias can be found in Section 2.6.4.2 of the full dossier assessment.

2.4.2.3 Results

Table 12 to Table 14 summarize the results at week 52 on the comparison of risankizumab with ustekinumab in patients with moderate to severe plaque psoriasis with inadequate response or intolerance to systemic therapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The outcomes on PASI 90 and PASI 75 are presented as supplementary information; remission (PASI 100) was primarily used for the derivation of the added benefit. The results on absence of symptoms on fingernails (NAPSI-finger 0) for patients with psoriasis on the fingernails at baseline (NAPSI-finger > 0) are additionally presented as supplementary information (see Section 2.6.4.3.2 of the full dossier assessment).

Forest plots of meta-analyses calculated by the Institute can be found in Appendix B.2 of the full dossier assessment. Tables on common AEs and discontinuation due to AEs are presented in Appendix B.3 of the full dossier assessment. Since the frequency of SAEs occurring in the studies UltIMMa-1 and UltIMMa-2 was low and there were no events that occurred in at least 5% of patients in one study arm, the frequencies of SAEs are not presented.

Table 12: Results (mortality, morbidity, health-related quality of life, side effects, 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					
Mortality					
All-cause mortality					
UltIMMa-1	100	0 (0)	34	0 (0)	NC
UltIMMa-2	90	0 (0)	36	0 (0)	NC
Total					NC
Morbidity					
Skin symptoms					
Remission (PASI 100)[b]					
UltIMMa-1	100	64 (64.0)	34	5 (14.7)	4.47 [1.97; 10.14]; < 0.001
UltIMMa-2	90	56 (62.2)	36	11 (30.6)	2.07 [1.24; 3.47]; 0.006
Total[c]					2.80 [1.80; 4.36]; < 0.001
Remission (PASI 100) – sensitivity analysis (LOCF), supplementary information[d]					
UltIMMa-1	*100*	*64 (64.0)*	*34*	*6 (17.6)*	*3.71 [1.78; 7.76]; < 0.001*
UltIMMa-2	*90*	*58 (64.4)*	*35*	*12 (34.3)*	*1.92 [1.19; 3.10]; 0.007*
Total[c]					*2.49 [1.66; 3.75]; < 0.001*
Remission (PASI 100) – sensitivity analysis (MI), supplementary information[e]					
UltIMMa-1	*100*	*64 (64.0)*	*34*	*5 (14.7)*	*4.46 [1.97; 10.12]; < 0.001*
UltIMMa-2	*90*	*56.2 (62.4)*	*36*	*11 (30.6)*	*2.08 [1.24; 3.48]; 0.005*
Total[c]					*2.81 [1.80; 4.36]; < 0.001*

(continued)

Table 12: Results (mortality, morbidity, health-related quality of life, side effects, 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**
PASI 90 (supplementary information)[b]					
UltIMMa-1	*100*	*86 (86.0)*	*34*	*13 (38.2)*	*2.27 [1.47; 3.50]; < 0.001*
UltIMMa-2	*90*	*74 (82.2)*	*36*	*17 (47.2)*	*1.74 [1.21; 2.48]; 0.003*
Total[c]					*1.97 [1.49; 2.60]; < 0.001*
PASI 75 (supplementary information)[b]					
UltIMMa-1	*100*	*92 (92.0)*	*34*	*25 (73.5)*	*1.25 [1.01; 1.54]; 0.036*[f]
UltIMMa-2	*90*	*85 (94.4)*	*36*	*28 (77.8)*	*1.21 [0.96; 1.53]; 0.110*
Total[c]					*1.24 [1.08; 1.43]; 0.002*
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 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 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

(continued)

Table 12: Results (mortality, morbidity, health-related quality of life, side effects, 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 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
Further patient-reported symptoms (particularly scaling, cracking, bleeding)	No data recorded[g]				
Absence of symptoms on hands and feet (PPASI 0)	No usable data[h]				
Absence of symptoms on fingernails (NAPSI-finger 0)	No usable data[i]				
Absence of symptoms on the scalp (PSSI 0)[b, j]					
UltIMMa-1	91	77 (84.6)	29	15 (51.7)	1.60 [1.11; 2.31]; 0.011
UltIMMa-2	80	66 (82.5)	28	17 (60.7)	1.37 [1.00; 1.87]; 0.052
Total[c]					1.48 [1.17; 1.88]; 0.001
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[c]					1.47 [1.16; 1.86]; 0.001
Side effects					
AEs (supplementary information)					
UltIMMa-1	*100*	*71 (71.0)*	*34*	*28 (82.4)*	–
UltIMMa-2	*90*	*63 (70.0)*	*36*	*28 (77.8)*	–

(continued)

Table 12: Results (mortality, morbidity, health-related quality of life, side effects, 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
Side effects					
SAEs					
UltIMMa-1	100	8 (8.0)	34	3 (8.8)	0.91 [0.25; 3.22]; 0.880
UltIMMa-2	90	6 (6.7)	36	3 (8.3)	0.80 [0.21; 3.03]; 0.742
Total[c]					0.85 [0.34; 2.14]; 0.738
Discontinuation due to AEs					
UltIMMa-1	100	1 (1.0)	34	1 (2.9)	0.34 [0.02; 5.29]; 0.441
UltIMMa-2	90	0 (0.0)	36	1 (2.8)	0.14 [0.01; 3.25]; 0.218
Total[c]					0.18 [0.02; 1.95]; 0.159
Infections and infestations (SOC, AE)					
UltIMMa-1	100	47 (47.0)	34	16 (47.1)	1.00 [0.66; 1.51]; > 0.999[k]
UltIMMa-2	90	43 (47.8)	36	17 (47.2)	1.01 [0.67; 1.52]; 0.978[k]
Total					1.01 [0.75; 1.34]; 0.971[l]

(continued)

Table 12: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: risankizumab vs. ustekinumab (research question B) (continued)

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: Calculated from IPD meta-analysis with fixed effect.
d: Missing values imputed using LOCF.
e: Missing values imputed using MI.
f: The model did not converge, so the model was calculated without stratification variables.
g: The company's dossier contained no data for further outcomes of patient-reported symptoms (particularly scaling, cracking and bleeding) (see Section 2.6.4.3.2 of the full dossier assessment).
h: Only patients with palmoplantar involvement at baseline (PPASI > 0) were analysed. This was only about 1 third of the ITT population (see Table 8).
i: Only patients with fingernail involvement at baseline (NAPSI-finger > 0) were analysed. This was only about 64% of the ITT population (see Table 8). The results for patients with nail psoriasis at baseline are presented as supplementary information (see Table 13).
j: Only patients with scalp involvement at baseline (PSSI > 0) were analysed. This was > 80% of the ITT population (UltIMMa-1: 91.0% in the risankizumab arm and 85.3% in the ustekinumab arm; UltIMMa-2: 88.9% in the risankizumab arm and 77.8% in the ustekinumab arm).
k: Institute's calculation; asymptotic 95% CI; p-value from unconditional exact test (CSZ method according to [12]).
l: Institute's calculation, meta-analysis with fixed effect according to Mantel and Haenszel.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; DLQI: Dermatology Life Quality Index; IPD: individual patient data; ITT: intention to treat; LOCF: last observation carried forward; MI: multiple imputation; N: number of analysed patients; n: number of patients with (at least one) event; NAPSI: Nail Psoriasis Severity Index; NC: not calculable; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PPASI: Palmoplantar Psoriasis Area and Severity Index; PSS: Psoriasis Symptom Scale; PSSI: Psoriasis Scalp Severity Index; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 13: Supplementary presentation of the results for patients with nail psoriasis at study start (morbidity [NAPSI], dichotomous) – RCT, direct comparison: risankizumab vs. ustekinumab (research question B)

Outcome category **Outcome**	**Risankizumab**		**Ustekinumab**		**Risankizumab vs. ustekinumab**
Time point **Study**	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI][a]; p-value**
Week 52					
Morbidity					
Absence of symptoms on fingernails (NAPSI-finger 0)[b], supplementary presentation					
UltIMMa-1	*68*	*34 (50.0)*	*25*	*10 (40.0)*	*1.22 [0.72; 2.06]; 0.454*
UltIMMa-2	*50*	*31 (62.0)*	*22*	*9 (40.9)*	*1.52 [0.89; 2.60]; 0.124*
Total[c]					*1.38 [0.95; 2.01]; 0.090*

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: Calculated from meta-analysis.

CI: confidence interval; N: number of analysed patients; n: number of patients with (at least one) event; NAPSI: Nail Psoriasis Severity Index; NRI: non-responder imputation; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 14: Results (morbidity, continuous) – RCT, direct comparison: risankizumab vs. ustekinumab (research question B)

Outcome category Outcome Study	Risankizumab			Ustekinumab			Risankizumab vs. ustekinumab
	N[a]	Values at baseline mean (SD)	Change at week 52 mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change at week 52 mean (SE)[b]	MD [95% CI]; p-value[b]
Morbidity							
Health status (EQ-5D VAS[c])							
UltIMMa-1	99	65.95 (23.07)	12.12 (1.63)	33	70.67 (18.16)	6.14 (2.45)	5.98 [0.84; 11.13]; 0.023
UltIMMa-2	90	66.46 (21.72)	15.80 (1.58)	34	70.50 (21.81)	13.82 (2.48)	1.97 [−3.37; 7.32]; 0.466
Total[d]							4.30 [0.56; 8.04]; 0.025 Hedges' g: 0.32 [0.04; 0.60]

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b: Effect estimation based on an ANCOVA model with treatment, stratification variables and baseline value as covariables; for the meta-analysis, the variable study is additionally included in the model as a fixed effect. Missing values were imputed using LOCF.
c: A positive change from the start until the end of the study indicates improvement; a positive group difference indicates an advantage for risankizumab.
d: Calculated from meta-analysis.

ANCOVA: analysis of covariance; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; LOCF: last observation carried forward; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Based on the available data, at most proof, e.g. of an added benefit, can be derived from the meta-analysis of the studies ULtIMMa-1 and ULtIMMa-2 for the following outcomes: all-cause mortality, remission (PASI 100), SAEs, discontinuation due to AEs, and infections and infestations. For all other outcomes for which usable data are available, at most indications, e.g. of an added benefit, can be determined due to the high risk of bias and lacking sensitivity analyses (see Section 2.4.2.2 and Section 2.6.4.3.1 of the full dossier assessment).

Mortality

All-cause mortality

No deaths occurred in the studies UltIMMa-1 and UltIMMa-2 until week 52. There was no hint of an added benefit of risankizumab in comparison with ustekinumab for all-cause mortality; an added benefit is therefore not proven.

The company also described that no deaths occurred in both UltIMMa studies in the relevant subpopulation. The company claimed no added benefit.

Morbidity

Remission (PASI 100)

The meta-analysis of the studies showed a statistically significant effect in favour of risankizumab for the outcome "remission" determined with the PASI 100.

Due to the high proportions of imputed values and their differences between the treatment groups, the results had a high risk of bias, however. For this reason, the results of sensitivity analyses (LOCF and MI) were additionally considered for the responder analyses at week 52 (see Section 2.6.4.3.1 of the full dossier assessment). The results of these analyses were of comparable magnitude and still showed a statistically significant difference in favour of risankizumab. The result was therefore robust, so that a high certainty of results was assumed despite the outcome-specific high risk of bias.

Hence, there was proof of added benefit of risankizumab versus ustekinumab for the outcome "remission".

This concurs with the assessment of the company, which used both analyses on the proportion of patients with remission and on the time to achieving remission.

Patient-reported absence of symptoms (outcomes "PSS itching", "PSS pain" and "PSS burning")

The meta-analysis showed a statistically significant effect in favour of risankizumab for each of the outcomes "PSS itching", "PSS pain" and "PSS burning". However, there was an effect modification by the characteristic "age" for all 3 outcomes (see Section 2.4.2.4). As a result, there was no hint of an added benefit of risankizumab in comparison with ustekinumab for patients under the age of 40 years and for patients aged 65 years and older; an added benefit is therefore not proven. Under consideration of the high risk of bias, there was an indication of an added benefit of risankizumab in comparison with ustekinumab for each of these outcomes for patients aged between 40 and 64 years.

This deviates from the assessment of the company, which did not consider effect modifications in the derivation of the added benefit. From the meta-analysis of the studies UltIMMa-1 and UltIMMa-2, the company derived proof of an added benefit for the total subpopulation for each of the outcomes "PSS itching", "PSS pain" and "PSS burning" of the patient-reported absence of symptoms. In the derivation of the added benefit, it considered the analyses on the proportion of patients with absence of symptoms, and for the outcome "PSS itching" additionally the time to achieving absence of symptoms.

Patient-reported absence of symptoms (PSS redness)

The meta-analysis showed a statistically significant effect in favour of risankizumab for the outcome "PSS redness". However, there was an effect modification by the characteristic "previous biologic treatment" (see Section 2.4.2.4). As a result, there was no hint of an added benefit of risankizumab in comparison with ustekinumab for patients without previous biologic

treatment; an added benefit is therefore not proven. Under consideration of the high risk of bias, there was an indication of an added benefit of risankizumab in comparison with ustekinumab for this outcome for patients pretreated with biologics.

This deviates from the assessment of the company, which did not consider effect modifications in the derivation of the added benefit. From the meta-analysis of the studies UltIMMa-1 and UltIMMa-2, the company derived proof of an added benefit for the total subpopulation for the outcome "PSS redness".

Further patient-reported symptoms (particularly scaling, cracking and bleeding)

The company's dossier contained no data for further outcomes of patient-reported symptoms (particularly scaling, cracking and bleeding) (see Section 2.6.4.3.2 of the full dossier assessment).

There was no hint of an added benefit of risankizumab in comparison with ustekinumab for further outcomes of patient-reported symptoms (particularly scaling, cracking and bleeding); an added benefit is therefore not proven.

The company did not record any data on further patient-reported symptoms and therefore did not address this issue in the dossier.

Absence of symptoms on hands and feet (PPASI 0)

There were no usable data for the outcome "absence of symptoms on hands and feet (PPASI 0)". For its analyses, the company used the subpopulation of patients with palmoplantar psoriasis (PPASI > 0) at baseline. These analyses did not consider an important proportion of the randomized patients and were therefore unsuitable for the derivation of the added benefit (see Section 2.6.4.3.2 of the full dossier assessment).

There was no hint of an added benefit of risankizumab in comparison with ustekinumab for the outcome "absence of symptoms on hands and feet (PPASI 0)"; an added benefit is therefore not proven.

This deviates from the assessment of the company insofar as the company considered the results on the proportion of patients with PPASI 0 from the meta-analysis of the studies UltIMMa-1 and UltIMMa-2, but then did not use the outcome for the derivation of the added benefit.

Absence of symptoms on the scalp (PSSI 0)

The meta-analysis of the studies showed a statistically significant difference in favour of risankizumab for the outcome "absence of symptoms on the scalp (PSSI 0)". Under consideration of the high risk of bias, there was an indication of an added benefit of risankizumab in comparison with ustekinumab for this outcome.

This deviates from the assessment of the company, which derived proof of an added benefit from the meta-analysis of the studies UltIMMa-1 and UltIMMa-2.

Absence of symptoms on fingernails (NAPSI-finger 0)

There were no usable data for the outcome "absence of symptoms on fingernails (NAPSI-finger 0)". For its analyses, the company used the subpopulation of patients with nail psoriasis (NAPSI-finger > 0) at baseline. These analyses did not consider an important proportion of the randomized patients and were therefore unsuitable for the derivation of the added benefit (see Section 2.6.4.3.2 of the full dossier assessment).

There was no hint of an added benefit of risankizumab in comparison with ustekinumab for the outcome "absence of symptoms on fingernails (NAPSI-finger 0)"; an added benefit is therefore not proven.

This deviates from the assessment of the company insofar as the company considered the results on NAPSI-finger 0 from the meta-analysis of the studies UltIMMa-1 and UltIMMa-2, but then did not use the outcome for the derivation of the added benefit.

Health status (EQ-5D VAS)

A statistically significant difference in favour of risankizumab was shown for the outcome "health status" measured with the EQ-5D VAS. In addition, there was an effect modification by the characteristic "sex" for this outcome (see Section 2.4.2.4). As a result, there was no hint of an added benefit of risankizumab in comparison with ustekinumab for women; an added benefit for women is therefore not proven. Under consideration of the high risk of bias, there was an indication of an added benefit of risankizumab in comparison with ustekinumab for this outcome for men.

This deviates from the assessment of the company, which did not consider effect modifications in the derivation of the added benefit. The company considered the results on health status from the meta-analysis of the studies UltIMMa-1 and UltIMMa-2, but did not use the outcome for the derivation of the added benefit.

Health-related quality of life

DLQI (0 or 1)

The meta-analysis of the studies showed a statistically significant difference in favour of risankizumab for the outcome "health-related quality of life" measured with the DLQI. Under consideration of the high risk of bias, there was an indication of an added benefit of risankizumab in comparison with ustekinumab for this outcome.

This deviates from the assessment of the company, which derived proof of an added benefit from the meta-analysis of the studies UltIMMa-1 and UltIMMa-2. Besides the analyses on the proportion of patients with a DLQI (0 or 1), it also considered the time to achieving a DLQI (0 or 1) for the derivation of the added benefit.

Side effects

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

The meta-analysis of the studies showed no statistically significant differences between the treatment groups for the outcomes "SAEs", "discontinuation due to AEs", and "infections and infestations". Consequently, for the outcomes "SAEs", "discontinuation due to AEs", and "infections and infestations", there was no hint of greater or lesser harm from risankizumab in comparison with ustekinumab; greater or lesser harm is therefore not proven.

For the outcomes "SAEs" and "discontinuation due to AEs", this concurs with the assessment of the company, which derived no added benefit for these outcomes from the meta-analysis of the studies UltIMMa-1 and UltIMMa-2. The company did not include the outcome "infections and infestations" in its assessment.

2.4.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered in the present benefit assessment (see also Section 2.6.4.3.4 of the full dossier assessment):

- sex (men/women)
- age (< 40/≥ 40 to < 65/≥ 65 years)
- ethnicity (white/non-white)
- disease severity (sPGA 3/4)
- previous biologic treatment (yes/no)

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. For binary data, there must be 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant and relevant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 15 shows the results of the subgroup analyses.

Table 15: Subgroups (morbidity, dichotomous) – RCT, direct comparison: risankizumab vs. ustekinumab (research question B)

Outcome Characteristic Study Subgroup	Risankizumab N	Risankizumab Patients with event n (%)	Ustekinumab N	Ustekinumab Patients with event n (%)	Risankizumab vs. ustekinumab RR [95% CI][a]	Risankizumab vs. ustekinumab p-value[a]
Morbidity						
Patient-reported absence of symptoms – PSS itching 0						
Age						
UltIMMa-1						
< 40 years	22	17 (77.3)	12	7 (58.3)	1.32 [0.78; 2.25]	0.298
≥ 40 – < 65 years	70	47 (67.1)	19	4 (21.1)	3.19 [1.31; 7.74]	0.010
≥ 65 years	8	5 (62.5)	3	2 (66.7)	0.94 [0.36; 2.46]	0.896
UltIMMa-2						
< 40 years	34	27 (79.4)	10	8 (80.0)	0.99 [0.70; 1.41]	0.967
≥ 40 – < 65 years	51	35 (68.6)	21	4 (19.0)	3.60 [1.46; 8.87]	0.005
≥ 65 years	5	5 (100.0)	5	2 (40.0)	ND	
Total[b]					Interaction:	0.004
< 40 years					1.12 [0.81; 1.55]	0.501
≥ 40 – < 65 years					3.40 [1.80; 6.39]	< 0.001
≥ 65 years					1.83 [0.24; 14.04]	0.561
Patient-reported absence of symptoms – PSS pain 0						
Age						
UltIMMa-1						
< 40 years	22	19 (86.4)	12	8 (66.7)	1.30 [0.84; 2.00]	0.241
≥ 40 – < 65 years	70	57 (81.4)	19	7 (36.8)	2.21 [1.21; 4.02]	0.009
≥ 65 years	8	6 (75.0)	3	2 (66.7)	1.12 [0.46; 2.75]	0.796
UltIMMa-2						
< 40 years	34	28 (82.4)	10	9 (90.0)	0.92 [0.71; 1.19]	0.501
≥ 40 – < 65 years	51	42 (82.4)	21	8 (38.1)	2.16 [1.24; 3.78]	0.007
≥ 65 years	5	5 (100.0)	5	4 (80.0)	ND	
Total[b]					Interaction:	0.008
< 40 years					1.07 [0.81; 1.41]	0.633
≥ 40 – < 65 years					2.18 [1.45; 3.29]	< 0.001
≥ 65 years					1.23 [0.44; 3.40]	0.692

(continued)

Table 15: Subgroups (morbidity, dichotomous) – RCT, direct comparison: risankizumab vs. ustekinumab (research question B) (continued)

Outcome Characteristic / Study / Subgroup	Risankizumab N	Risankizumab Patients with event n (%)	Ustekinumab N	Ustekinumab Patients with event n (%)	Risankizumab vs. ustekinumab RR [95% CI][a]	Risankizumab vs. ustekinumab p-value[a]
Morbidity						
Patient-reported absence of symptoms – PSS burning 0						
Age						
UltIMMa-1						
< 40 years	22	19 (86.4)	12	9 (75.0)	1.15 [0.80; 1.66]	0.450
≥ 40 – < 65 years	70	59 (84.3)	19	11 (57.9)	1.46 [0.98; 2.16]	0.063
≥ 65 years	8	7 (87.5)	3	3 (100.0)	ND	
UltIMMa-2						
< 40 years	34	28 (82.4)	10	9 (90.0)	0.92 [0.71; 1.19]	0.501
≥ 40 – < 65 years	51	44 (86.3)	21	9 (42.9)	2.01 [1.21; 3.34]	0.007
≥ 65 years	5	5 (100.0)	5	3 (60.0)	ND	
Total[b]					Interaction:	0.040
< 40 years					1.02 [0.80; 1.30]	0.876
≥ 40 – < 65 years					1.70 [1.24; 2.35]	0.001
≥ 65 years					1.23 [0.80; 1.89][c]	0.344
Patient-reported absence of symptoms – PSS redness 0						
Previous biologic treatment						
UltIMMa-1						
Yes	51	35 (68.6)	15	4 (26.7)	2.57 [1.09; 6.08]	0.031
No	49	33 (67.3)	19	8 (42.1)	1.60 [0.91; 2.81]	0.102
UltIMMa-2						
Yes	47	33 (70.2)	16	3 (18.8)	3.74 [1.33; 10.56]	0.013
No	43	35 (81.4)	20	12 (60.0)	1.36 [0.92; 1.99]	0.121
Total[b]					Interaction:	0.029
Yes					3.07 [1.58; 5.98]	< 0.001
No					1.44 [1.04; 1.99]	0.027

a: From generalized linear model with treatment and study as covariables with a log link for the calculation of the RR.
b: Calculated from meta-analysis.
c: The model did not converge, so the model was calculated without study as covariable.
CI: confidence interval; N: number of analysed patients; n: number of patients with (at least one) event; ND: no data; PASI: Psoriasis Area and Severity Index; PPASI: Palmoplantar Psoriasis Area and Severity Index; PSS: Psoriasis Symptom Scale; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 16: Subgroups (morbidity, continuous) – RCT, direct comparison: risankizumab vs. ustekinumab (research question B)

Outcome Characteristic	Risankizumab			Ustekinumab			Risankizumab vs. ustekinumab
Study Subgroup	N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)[b]	MD [95% CI]; p-value[b]
Morbidity							
Health status (EQ-5D VAS)[c]							
Sex							
UltIMMa-1							
Women	28	62.00 (23.39)	16.69 (2.56)	8	70.38 (24.47)	11.45 (4.82)	5.24 [−5.92; 16.39]; 0.347
Men	71	67.51 (22.92)	14.62 (1.54)	25	70.76 (16.28)	8.13 (2.61)	6.48 [0.46; 12.50]; 0.035
UltIMMa-2							
Women	32	64.94 (21.95)	13.34 (2.66)	11	73.18 (24.45)	20.93 (4.56)	−7.59 [−18.32; 3.14]; 0.161
Men	58	67.29 (21.74)	17.83 (1.55)	23	69.22 (20.89)	10.05 (2.46)	7.78 [1.99; 13.56]; 0.009
Total[d]						Interaction:	p-value = 0.020
Women							−1.94 [−9.82; 5.94]; 0.625
Men							7.04 [2.84; 11.24]; 0.001
							Hedges' g: 0.55 [0.22; 0.89]

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b: Effect estimation based on an ANCOVA model with treatment, stratification variables and baseline value as covariables; for the meta-analysis, the variable study is additionally included in the model as a fixed effect. Missing values were imputed using LOCF.
c: A positive change from the start until the end of the study indicates improvement; a positive group difference indicates an advantage for risankizumab.
d: Calculated from meta-analysis.
ANCOVA: analysis of covariance; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; LOCF: last observation carried forward; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Morbidity

Patient-reported absence of symptoms (outcomes "PSS itching", "PSS pain" and "PSS burning")

The meta-analysis of the studies showed an effect modification by the characteristic "age" for each of the outcomes "PSS itching", "PSS pain" and "PSS burning" of the patient-reported absence of symptoms. No statistically significant difference between the treatment arms was

shown for patients < 40 years and ≥ 65 years. As a result, there was no hint of an added benefit of risankizumab in comparison with ustekinumab for the outcomes "PSS itching", "PSS pain" and "PSS burning"; an added benefit is therefore not proven. A statistically significant effect in favour of risankizumab versus ustekinumab was shown for patients between 40 and 64 years of age. Under consideration of the high risk of bias, this resulted in an indication of an added benefit of risankizumab in comparison with ustekinumab for each of the outcomes "PSS itching", "PSS pain" and "PSS burning".

This deviates from the approach of the company, which did not consider effect modifications in the derivation of the added benefit.

Patient-reported absence of symptoms (PSS redness)

The meta-analysis of the studies showed an effect modification by the characteristic "previous biologic treatment" for the outcome "PSS redness". A statistically significant difference between the treatment arms was shown for patients without previous biologic treatment. This difference was no more than marginal, however. Hence, there was no hint of an added benefit of risankizumab in comparison with ustekinumab; an added benefit is therefore not proven. A statistically significant and relevant effect in favour of risankizumab versus ustekinumab was shown for patients with previous biologic treatment. Under consideration of the high risk of bias, this resulted in an indication of an added benefit of risankizumab in comparison with ustekinumab.

This deviates from the approach of the company, which did not consider effect modifications in the derivation of the added benefit.

Health status (EQ-5D VAS)

The meta-analysis of the studies showed an effect modification by the characteristic "sex" for the outcome "health status" measured with the EQ-5D VAS. No statistically significant difference between the treatment arms was shown for women. As a result, there was no hint of an added benefit of risankizumab in comparison with ustekinumab for women; an added benefit for women is therefore not proven. A statistically significant difference in favour of risankizumab versus ustekinumab was shown for men. Since the confidence interval of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. This resulted in an indication of an added benefit of risankizumab in comparison with ustekinumab for men.

This deviates from the approach of the company, which did not consider effect modifications in the derivation of the added benefit.

2.4.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4.2 (see Table 17).

Determination of the outcome category for the outcomes on morbidity

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Determination of the outcome category for the outcome "remission (PASI 100)"

Psoriasis is a chronic disease which, due to the location of the lesions and the manifestation of its symptoms, can be very burdensome and seriously affect the patients. Hence, the allocation of the outcome "remission (PASI 100)" to an outcome category depends on the patients' initial situation, and particularly on the severity and the grade of impairment from the symptoms measured with PASI (psoriatic plaque redness, thickness and scaling).

The data recorded in the beginning of the study were used for assessing the severity of the symptoms. The median PASI score at baseline was below 20 in all study arms (UltIMMa-1: 18.05 in both study arms; UltIMMa-2: 18.50 in the risankizumab arm versus 16.40 in the ustekinumab arm). Hence, the PASI scores for the majority of the participants tended to be in a non-serious range [13,14]. The outcome "remission (PASI 100)" for these patients was therefore allocated to the category of non-serious/non-severe symptoms/late complications.

This allocation deviates from the assessment of the company insofar as the company did not allocate the outcome "remission" to any outcome category.

Determination of the outcome category for the outcomes on patient-reported absence of symptoms (outcomes "PSS itching", "PSS redness", "PSS pain" and "PSS burning")

As already described for the outcome "remission (PASI 100)", the allocation of the outcomes "PSS itching", "PSS redness", "PSS pain" and "PSS burning" to an outcome category depends on the patients' initial situation. The respective symptoms (itching, redness, pain and burning) are evaluated on a 5-point scale, where 0 stands for no symptoms and 4 for very severe symptoms. However, since there was not enough information about the initial situation of the patients at baseline and the company also did not provide any information about the classification of the severity of the individual symptoms, the outcomes "PSS itching", "PSS redness", "PSS pain" and "PSS burning" were allocated to the category of non-serious/non-severe symptoms/late complications.

This allocation deviates from the assessment of the company insofar as the company did not allocate the outcomes “PSS itching, “PSS redness”, “PSS pain” and “PSS burning” to any outcome category.

Determination of the outcome category for the outcome “absence of symptoms on the scalp (PSSI 0)”

As with the outcome “remission (PASI 100)” described above, the allocation of the outcome “absence of symptoms on the scalp” to an outcome category depends on the patients’ initial situation. The PSSI is an instrument for the assessment of scalp psoriasis, which evaluates the symptoms of redness, induration and scaling, and the proportion of affected scalp. The PSSI score can range from 0 to 72.

However, for the assessment of the severity of scalp psoriasis, there is no information available for the PSSI as to when it can be classified as severe. Since the company also did not provide any information on the classification of the severity grade, the outcome “absence of symptoms on the scalp” determined with PSSI 0 was allocated to the category of non-serious/non-severe symptoms/late complications.

This allocation deviates from the assessment of the company insofar as the company did not allocate the outcome “absence of symptoms on the scalp” to any outcome category.

Determination of the outcome category for the outcome “health status (EQ-5D VAS)”

It could not be inferred from the dossier that the outcome “health status” determined with the VAS of the EQ-5D could be allocated to severe or serious symptoms. Since the company also did not provide any information on the classification of the severity grade, the outcome “health status” was allocated to the category of non-serious/non-severe symptoms/late complications.

This allocation deviates from the assessment of the company insofar as the company did not allocate the outcome “health status” determined with the EQ-5D VAS to any outcome category.

Table 17: Extent of added benefit at outcome level: risankizumab vs. ustekinumab (research question B)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Risankizumab vs. ustekinumab** **Proportion of events (%) or MD at week 52** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser benefit/added benefit not proven
Morbidity		
Remission (PASI 100)		
Main analysis – NRI	62.2–64.0% vs. 14.7–30.6%[c] RR: 2.80 [1.80; 4.36]; RR: 0.36 [0.23; 0.56][d] p < 0.001	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 added benefit, extent: “considerable”
Sensitivity analysis – LOCF	64.0–64.4% vs. 17.6–34.3%[c] RR: 2.49 [1.66; 3.75]; RR: 0.40 [0.27; 0.60][d] p < 0.001	
Sensitivity analysis – MI	62.4–64.0% vs. 14.7–30.6%[c] RR: 2.81 [1.8; 4.36]; RR: 0.36 [0.23; 0.56][d] p < 0.001 probability: “proof”	
PSS itching 0		
Age		
< 40 years	77.3–79.4% vs. 58.3–80.0%[c] RR: 1.12 [0.81; 1.55]; p = 0.501	Lesser benefit/added benefit not proven
≥ 40 – < 65 years	67.1–68.6% vs. 19.0–21.1%[c] RR: 3.40 [1.80; 6.39]; RR: 0.29 [0.16; 0.56][d] p < 0.001 probability: “indication”	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 added benefit, extent: “considerable”
≥ 65 years	62.5–100.0% vs. 40.0–66.7%[c] RR: 1.83 [0.24; 14.04]; p = 0.561	Lesser benefit/added benefit not proven

(continued)

Table 17: Extent of added benefit at outcome level: risankizumab vs. ustekinumab (research question B) (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Risankizumab vs. ustekinumab** **Proportion of events (%) or MD at week 52** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
PSS pain 0 Age < 40 years	82.4–86.4% vs. 66.7–90.0%[c] RR: 1.07 [0.81; 1.41]; p = 0.633	Lesser benefit/added benefit not proven
≥ 40 – < 65 years	81.4–82.4% vs. 36.8–38.1%[c] RR: 2.18 [1.45; 3.29]; RR: 0.46 [0.30; 0.69][d] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
≥ 65 years	75.0–100.0% vs. 66.7–80.0%[c] RR: 1.23 [0.44; 3.40]; p = 0.692	Lesser benefit/added benefit not proven
PSS redness 0 Previous biologic treatment Yes	68.6–70.2% vs. 18.8–26.7%[c] RR: 3.07 [1.58; 5.98]; RR: 0.33 [0.17; 0.63][d] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
No	67.3–81.4% vs. 42.1–60.0%[c] RR: 1.44 [1.04; 1.99]; RR: 0.69 [0.50; 0.96][d] p = 0.027	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[e]

(continued)

Table 17: Extent of added benefit at outcome level: risankizumab vs. ustekinumab (research question B) (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Risankizumab vs. ustekinumab** **Proportion of events (%) or MD at week 52** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
PSS burning 0 Age < 40 years	82.4–86.4% vs. 75.0–90.0%[c] RR: 1.02 [0.80; 1.30]; p = 0.876	Lesser benefit/added benefit not proven
≥ 40 – < 65 years	84.3–86.3% vs. 42.9–57.9%[c] RR: 1.70 [1.24; 2.35]; RR: 0.59 [0.43; 0.81][d] p = 0.001 probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
≥ 65 years	87.5–100.0% vs. 60.0–100.0%[c] RR: 1.23 [0.80; 1.89]; p = 0.344	Lesser benefit/added benefit not proven
Further patient-reported symptoms (particularly scaling, cracking and bleeding)	No data	Lesser benefit/added benefit not proven
Absence of symptoms on hands and feet (PPASI 0)	No usable data	Lesser benefit/added benefit not proven
Absence of symptoms on fingernails (NAPSI-finger 0)	No usable data	Lesser benefit/added benefit not proven
Absence of symptoms on the scalp (PSSI 0)	82.5–84.6% vs. 51.7–60.7%[c] RR: 1.48 [1.17; 1.88]; RR: 0.68 [0.53; 0.85][d] p = 0.001 probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Health status (EQ-5D VAS) Sex Women	62.00–64.94 vs. 70.38–73.18[c] MD: –1.94 [–9.82; 5.94]; p = 0.625	Lesser benefit/added benefit not proven
Men	67.29–67.51 vs. 69.22–70.76[c] MD: 7.04 [2.84; 11.24]; p = 0.001 Hedges' g: 0.55 [0.22; 0.89][f] probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"

(continued)

Table 17: Extent of added benefit at outcome level: risankizumab vs. ustekinumab (research question B) (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Risankizumab vs. ustekinumab** **Proportion of events (%) or MD at week 52** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
DLQI (0 or 1)	75.0–76.7% vs. 47.2–55.9%[c] RR: 1.47 [1.16; 1.86]; RR: 0.68 [0.54; 0.86][d] p = 0.001 probability: "indication"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
Side effects		
SAEs	6.7–8.0% vs. 8.3–8.8%[c] RR: 0.85 [0.34; 2.14]; p = 0.738	Greater/lesser harm not proven
Discontinuation due to AEs	0–1.0% vs. 2.8–2.9%[c] RR: 0.18 [0.02; 1.95]; p = 0.159	Greater/lesser harm not proven
Infections and infestations (SOC, AEs)	47.0–47.8% vs. 47.1–47.2%[c] RR: 1.01 [0.75; 1.34]; p = 0.971	Greater/lesser harm not proven

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the confidence interval (CI_u).
c: Minimum and maximum proportions of events or mean changes in each treatment arm in the included studies.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
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, the presence of a relevant effect cannot be derived.

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; LOCF: last observation carried forward; MD: mean difference; MI: multiple imputation; NAPSI: Nail Psoriasis Severity Index; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PPASI: Palmoplantar Psoriasis Area and Severity Index; PSS: Psoriasis Symptom Scale; PSSI: Psoriasis Scalp Severity Index; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 18 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of risankizumab in comparison with ustekinumab (research question B)

Positive effects	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: indication of an added benefit – extent: “considerable” ▪ patient-reported absence of symptoms (PSS pain 0) ▫ age ≥ 40 – < 65 years: indication 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): indication 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): indication of an added benefit – extent: “considerable”	–
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	

In the overall assessment, there are only positive effects – partly only in subgroups – with different certainty of results (proof or indication) for risankizumab in comparison with ustekinumab in the outcome categories of morbidity and health-related quality of life. The extent ranges from considerable to minor or is non-quantifiable. There is proof of considerable added benefit for remission (PASI 100).

In summary, there is therefore proof of considerable added benefit of risankizumab in comparison with ustekinumab for adult patients with moderate to severe plaque psoriasis with inadequate response or intolerance to systemic therapy.

This assessment concurs with that of the company.

2.4.4 List of included studies

UltIMMa-1

AbbVie. BI 655066 (risankizumab) compared to placebo and active comparator (ustekinumab) in patients with moderate to severe chronic plaque psoriasis: study details [online]. In: ClinicalTrials.gov. 18.06.2019 [Accessed: 06.08.2019]. URL: https://ClinicalTrials.gov/show/NCT02684370.

AbbVie. BI 655066 (risankizumab) compared to placebo and active comparator (ustekinumab) in patients with moderate to severe chronic plaque psoriasis: study results [online]. In: ClinicalTrials.gov. 18.06.2019 [Accessed: 06.08.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02684370?view=results.

AbbVie. ABBV-066 (risankizumab) versus ustekinumab and placebo comparators in a randomized double blind trial for maintenance use in moderate to severe plaque type psoriasis (UltIMMa-1): study UltIMMa-1; statistical analysis plan [unpublished]. 2017.

AbbVie. BI 655066/ABBV-066 (risankizumab) versus ustekinumab and placebo comparators in a randomized double blind trial for maintenance use in moderate to severe plaque type psoriasis: study UltIMMa-1; clinical study report [unpublished]. 2018.

AbbVie. BI 655066/ABBV-066 (risankizumab) versus ustekinumab and placebo comparators in a randomized double blind trial for maintenance use in moderate to severe plaque type psoriasis (UltIMMa-1): study UltIMMa-1; Zusatzanalysen [unpublished]. 2019.

Boehringer Ingelheim. BI 655066/ABBV-066 (risankizumab) versus ustekinumab and placebo comparators in a randomized double blind trIal for maintenance use in moderate to severe plaque type psoriasis (UltIMMa-1) [online]. In: EU Clinical Trials Register. [Accessed: 05.06.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-005117-23.

Boehringer Ingelheim. BI 655066/ABBV-066 (risankizumab) versus ustekinumab and placebo comparators in a randomized double blind trIal for maintenance use in moderate to severe plaque type psoriasis (UltIMMa-1): clinical trial results [online]. In: EU Clinical Trials Register. [Accessed: 05.06.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-005117-23/results.

Boehringer Ingelheim. BI 655066/ABBV-066 (risankizumab) versus ustekinumab and placebo comparators in a randomized double blind trial for maintenance use in moderate to severe plaque type psoriasis (UltIMMa-1): study UltIMMa-1; clinical trial protocol [unpublished]. 2016.

Gordon KB, Strober B, Lebwohl M, Augustin M, Blauvelt A, Poulin Y et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. Lancet 2018; 392(10148): 650-661.

UltIMMa-2

AbbVie. BI 655066 compared to placebo & active comparator (ustekinumab) in patients with moderate to severe chronic plaque psoriasis: study details [online]. In: ClinicalTrials.gov. 15.07.2019 [Accessed: 06.08.2019]. URL: https://ClinicalTrials.gov/show/NCT02684357.

AbbVie. BI 655066 compared to placebo & active comparator (ustekinumab) in patients with moderate to severe chronic plaque psoriasis: study results [online]. In: ClinicalTrials.gov. 15.07.2019 [Accessed: 06.08.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02684357.

AbbVie. BI 655066/ABBV-066 (risankizumab) versus ustekinumab and placebo comparators in a randomized double blind trial for maintenance use in moderate to severe plaque type psoriasis-2: study UltIMMa-2; clinical study report [unpublished]. 2017.

AbbVie. ABBV-066 (risankizumab) versus ustekinumab and placebo comparators in a randomized double blind trial for maintenance use in moderate to severe plaque type psoriasis-2 (UltIMMa-2): study UltIMMa-2; statistical analysis plan [unpublished]. 2017.

AbbVie. BI 655066/ABBV-066 (risankizumab) versus ustekinumab and placebo comparators in a randomized double blind trial for maintenance use in moderate to severe plaque type psoriasis-2: study UltIMMa-2; Zusatzanalysen [unpublished]. 2019.

Boehringer Ingelheim. BI 655066 versus ustekinumab and placebo comparators in a randomized double blind trial for maintenance use in moderate to severe plaque type psoriasis-2 (UltIMMa-2) [online]. In: EU Clinical Trials Register. [Accessed: 05.06.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-003622-13.

Boehringer Ingelheim. BI 655066 versus ustekinumab and placebo comparators in a randomized double blind trial for maintenance use in moderate to severe plaque type psoriasis-2 (UltIMMa-2): clinical trial results [online]. In: EU Clinical Trials Register. [Accessed: 05.06.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-003622-13/results.

Boehringer Ingelheim. BI 655066/ABBV-066 (risankizumab) versus ustekinumab and placebo comparators in a randomized double blind trial for maintenance use in moderate to severe plaque type psoriasis-2 (UltIMMa-2): study UltIMMa-2; clinical trial protocol [unpublished]. 2016.

Gordon KB, Strober B, Lebwohl M, Augustin M, Blauvelt A, Poulin Y et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. Lancet 2018; 392(10148): 650-661.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of risankizumab in comparison with the ACT is summarized in Table 19.

Table 19: 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 approach for deriving 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.

1. 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.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58.

3. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Risankizumab: zweckmäßige Vergleichstherapie. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/465/#zweckmaessige-vergleichstherapie].

4. AbbVie. A study to assess the efficacy of risankizumab compared to FUMADERM in subjects with moderate to severe plaque psoriasis who are naïve to and candidates for systemic therapy: study details [online]. In: ClinicalTrials.gov. 17.07.2018 [Accessed: 05.06.2019]. URL: https://ClinicalTrials.gov/show/NCT03255382.

5. AbbVie. A randomized, controlled, multicenter, open label study with blinded assessment of the efficacy of the humanized Anti-IL-23p19 risankizumab compared to FUMADERM in subjects with moderate to severe plaque psoriasis who are naïve to and candidates for systemic therapy [online]. In: EU Clinical Trials Register. [Accessed: 05.06.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-003718-28.

6. AbbVie. A randomized, controlled, multicenter, open label study with blinded assessment of the efficacy of the humanized Anti-IL-23p19 risankizumab compared to FUMADERM in subjects with moderate to severe plaque psoriasis who are naïve to and candidates for systemic therapy: study M16-178; clinical study report [unpublished]. 2018.

7. AbbVie. A randomized, controlled, multicenter, open label study with blinded assessment of the efficacy of the humanized Anti-IL-23p19 risankizumab compared to FUMADERM in subjects with moderate to severe plaque psoriasis who are naïve to and candidates for systemic therapy: study M16-178; clinical study protocol [unpublished]. 2017.

8. AbbVie. A randomized, controlled, multicenter, open label study with blinded assessment of the efficacy of the humanized Anti-IL-23p19 risankizumab compared to FUMADERM in subjects with moderate to severe plaque psoriasis who are naïve to and candidates for systemic therapy: study M16-178; statistical analysis plan [unpublished]. 2018.

9. AbbVie. A randomized, controlled, multicenter, open label study with blinded assessment of the efficacy of the humanized Anti-IL-23p19 risankizumab compared to FUMADERM in subjects with moderate to severe plaque psoriasis who are naïve to and candidates for systemic therapy: study M16-178; Zusatzanalysen [unpublished]. 2019.

10. AbbVie. Skyrizi 75 mg Injektionslösung in einer Fertigspritze: Fachinformation [online]. 04.2019 [Accessed: 14.05.2019]. URL: https://www.fachinfo.de.

11. Janssen. STELARA 45 mg/90 mg Injektionslösung, STELARA 45 mg/90 mg Injektionslösung in einer Fertigspritze: Fachinformation [online]. 07.2018 [Accessed: 14.05.2019]. URL: https://www.fachinfo.de.

12. 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.

13. Nast A, Amelunxen L, Augustin M, Boehncke W, Dressler C, Gaskins M et al. S3-Leitlinie zur Therapie der Psoriasis vulgaris: Update 2017 [online]. 10.2017 [Accessed: 28.02.2019]. URL: https://www.awmf.org/uploads/tx_szleitlinien/013-001l_S3_Therapie_Psoriasis-vulgaris_2017-12.pdf.

14. European Medicines Agency. Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis [online]. 18.11.2004 [Accessed: 28.02.2019]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003329.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-41-risankizumab-plaque-psoriasis-benefit-assessment-according-to-35a-social-code-book-v.12401.html.