IQWiG Reports – Commission No. A21-110

Bimekizumab (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 *Bimekizumab (Plaque-Psoriasis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 11 February 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Bimekizumab (plaque psoriasis) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
6 September 2021

Internal Commission No.
A21-110

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

- Heiko Traupe, University Hospital Münster, 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.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Marius Grosser.

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

IQWiG employees involved in the dossier assessment

- Ivona Djuric
- Ulrike Mikulić
- Lars Beckmann
- Tatjana Hermanns
- Florina Kerekes
- Cornelia Rüdig
- Dominik Schierbaum
- Volker Vervölgyi
- Pamela Wronski

Keywords: Bimekizumab, Psoriasis, Benefit Assessment, NCT03412747, NCT03536884

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 figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSA	body surface area
CI	confidence interval
DLQI	Dermatology Life Quality Index
EMA	European Medicines Agency
EQ-5D VAS	European Quality of Life – 5 Dimensions visual analogue scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HLGT	high level group term
IGA	Investigator's Global Assessment
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
mNAPSI	modified Nail Psoriasis Severity Index
OR	odds ratio
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
ppIGA	palmoplantar IGA
PSD	psoriasis diary
Q4W	every 4 weeks
Q8W	every 8 weeks
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SF-36	Short Form-36 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SOC	system organ class
SPC	Summary of Product Characteristics

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 bimekizumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 6 September 2021.

Research question

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

The research questions shown in Table 2 result from the ACTs specified by the G-BA.

Table 2: Research questions of the benefit assessment of bimekizumab

Research question	Therapeutic indication	ACT[a]
1	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**
2	Adult patients with moderate to severe plaque psoriasis with inadequate response or intolerance to prior systemic therapy	**Adalimumab** or brodalumab or guselkumab or infliximab or ixekizumab or risankizumab or **secukinumab** or ustekinumab

a. Presented is the respective ACT specified by the GBA. In cases where the ACT specified by the G-BA allows the company to 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 ease of presentation and reading, the running text of this benefit assessment uses the following designations for the research questions:

- Research question 1: adult patients who are not candidates for conventional treatment in the framework of initial systemic therapy
- Research question 2: adult patients with inadequate response or intolerance to prior systemic therapy

For both research questions, the company largely followed the G-BA's specification of the ACT. From the listed drugs, the company selected 2 (adalimumab and secukinumab). Given that the company did not restrict its search for studies relevant for the assessment to specific

drugs, but instead included all drugs specified by the G-BA, the company's prior selection did not exclude any potentially relevant studies.

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 added benefit.

Research question 1: adult patients who are not candidates for conventional treatment in the framework of initial systemic therapy

Study pool and study design

The study pool for the benefit assessment of bimekizumab in comparison with the ACT in adult patients who are not candidates for conventional treatment in the framework of initial systemic therapy comprises the RCTs BE SURE and BE RADIANT.

The BE SURE and BE RADIANT studies are randomized, active-control, double-blind trials in which 2 different dosing intervals of bimekizumab are compared with adalimumab (BE SURE) or secukinumab (BE RADIANT) in adults with moderate to severe plaque psoriasis (defined using body surface area [BSA] ≥ 10% , Psoriasis Area and Severity Index [PASI] ≥ 12, and Investigator's Global Assessment [IGA] ≥ 3 on a five-point scale).

The BE SURE study enrolled a total of 478 patients and randomized them in a 1:1:1 ratio to (a) bimekizumab treatment every 4 weeks (Q4W) (N = 158), (b) bimekizumab every 4 weeks followed by every 8 weeks from Week 16 (Q4W/Q8W) (N = 161), or (c) adalimumab followed by bimekizumab every 4 weeks from Week 24 (N = 159). The study design comprised a (2-week to 5-week) screening phase, followed by a 24-week active-control treatment phase (last dose of adalimumab in Week 23), and then a dose-blinded phase up to and including Week 56 (last dose of bimekizumab in Week 48 or 52). Due to the absence of a comparison with adalimumab, the dose-blinded phase (Week 24 through Week 56) is not relevant for the assessment and is therefore not considered further. Likewise, the bimekizumab Q4W arm was disregarded for the assessment due to the continuous 4-week dosing being in violation of approval.

The BE RADIANT study included a total of 743 patients who were randomly assigned at a 1:1 ratio to treatment with bimekizumab Q4W (N = 373) or secukinumab Q4W (N = 370). The study design includes a (2 to 5-week) screening phase, which is followed by a 48-week active-control, double-blind treatment phase (last dose of study medication in Week 44). After the first 16 treatment weeks, patients in the bimekizumab Q4W arm were randomized at a 1:2 ratio to bimekizumab treatment every 4 weeks (Q4W) or every 8 weeks (Q4W/Q8W). At the present data cut-off point, all patients had completed the visit at Week 48. The present assessment is based on the data from the active-control treatment phase. As was the case in the BE SURE study, the bimekizumab Q4W arm was disregarded in the assessment due to off-label dosing.

The co-primary outcomes of the BE SURE study are PASI 90 and an IGA score of 0 or 1 with simultaneous improvement by at least 2 scale points from baseline to Week 16. Patient-relevant secondary outcomes were remission (PASI 100) at Week 24 as well as outcomes on symptoms, health-related quality of life, and side effects. The primary outcome of the BE RADIANT study is remission (PASI 100) at Week 16. Patient-relevant secondary outcomes were remission (PASI 100 at Week 48) as well as outcomes on symptoms, health-related quality of life, and side effects.

For the BE SURE study, the company's dossier presents analyses of the data after 24 weeks of treatment based on the 1st data cut-off, 28 October 2019. For the BE RADIANT study, the company's dossier presents analyses of the data after 48 weeks of treatment based on the data cut-off 29 June 2020.

Studies' definition of severity of disease

In general, the severity of plaque psoriasis has not been clearly defined. The European Medicines Agency (EMA), for example, deems PASI > 10 or BSA > 10% a suitable operationalization of moderate to severe plaque psoriasis. The 2011 European consensus defines moderate to severe plaque psoriasis as "(BSA > 10 or PASI > 10) and Dermatology Life Quality Index (DLQI) > 10". Alongside the 2011 definition, the 2020 EuroGuiDerm guideline also offers several definitions without defining specific thresholds. The German S3 guideline, which is based on the EuroGuiDerm guideline, defines moderate to severe psoriasis in accordance with the European consensus, i.e. as "(BSA > 10 or PASI > 10) and DLQI > 10". In addition, the guideline specifies "upgrade criteria" in the presence of which psoriasis is classified as moderate to severe, irrespective of the above criteria.

The BE SURE and BE RADIANT studies defined moderate to severe plaque psoriasis as PASI ≥ 12 and BSA ≥ 10 and IGA ≥ 3. DLQI, another potential criterion for the severity of plaque psoriasis, was not used as an inclusion criterion. In both studies, the mean DLQI at baseline was between 8 and 10 and hence slightly below the threshold specified by the S3 guideline. However, both studies' patient populations included a large percentage of patients with involvement of the fingernails, palms and soles as well as the scalp.

In this light, while the severity definition used by the company disregarded the DLQI, it nevertheless adequately represented moderate to severe plaque psoriasis for the purposes of the present benefit assessment. With regard to PASI, the studies did not investigate patients with PASI scores between 10 and 12, who can also exhibit moderate to severe plaque psoriasis.

Subpopulation relevant for research question 1

Both studies included patients who the investigator deemed to be candidates for systemic therapy and/or phototherapy and for whom treatment with the respective ACT (adalimumab or secukinumab) was suitable according to the local Summary of Product Characteristics [SPC]. The populations of both studies were therefore more inclusive than the population of this assessment's research question 1 (patients who are not candidates for conventional treatment in

the framework of initial systemic therapy). Therefore, the company presented the results of a subpopulation in each case.

For research question 1, the company included only BE SURE and BE RADIANT participants who had not received any systemic psoriasis therapy prior to enrolment and who, according to the company, were not candidates for conventional treatment.

In accordance with the German S3 guideline, unsuitability of conventional systemic therapy stems from factors in the presence of which adequate treatment success of conventional systemic therapy is not to be expected. These criteria include, among others, particularly severe psoriasis (e.g. PASI ≥ 20) or particularly severe reduction of quality of life (e.g. DLQI ≥ 15) or severe fingernail or scalp involvement. Since the physician's assessment is additionally informed by individualized criteria, the G-BA recommends documenting clinical criteria in cases where a decision in favour of initial systemic therapy with non-conventional therapy is made based on individualized criteria upon the physician's discretion. The company's dossier provides no further specific criteria to define unsuitability of conventional systemic therapy. The company's dossier lists only the patient population's high overall disease burden as sufficient justification for inclusion in research question 1.

In summary, the information provided in the dossier and the company's aggregated data fail to clarify (1) whether each individual patient actually qualifies for inclusion in the subpopulation for research question 1 and (2) which specific criteria led to the decision in each case. No information is available on the physician's individual considerations and evaluations regarding the treatment decision in each case. This circumstance did not, however, lead to the exclusion of the studies. Instead, it was deemed possible to draw conclusions on the added benefit of bimekizumab in comparison with the ACT on the basis of the results of the studies. However, the uncertainties described were taken into account in the assessment of the certainty of conclusions.

In total, 45 patients in the bimekizumab arm and 49 patients in the adalimumab arm of the BE SURE study met the company's inclusion criteria for research question 1. For the BE RADIANT study, the same applied to 58 patients in the bimekizumab arm and 98 patients in the secukinumab arm.

Risk of bias and certainty of conclusions

The risk of bias across outcomes was rated as low for both studies. On the outcome level, the risk of bias was rated as high for all outcomes except all-cause mortality and the side effects outcomes (serious adverse events [SAEs], discontinuation due to AEs, infections and infestations [System Organ Class, SOC] as well as fungal infectious disorders [high level group term, HLGT]). No data on outcomes regarding further patient-reported absence of symptoms (particularly cracking and bleeding) are available for either study. No usable data are available for the outcomes of absence of symptoms on palms and soles (palmoplantar IGA [ppIGA] = 0)

and absence of symptoms on fingernails (modified Nail Psoriasis Severity Index [mNAPSI] 100) because all analyses included only patients with baseline mNAPSI 0 or ppIGA ≥ 2.

Due to the difference in follow-up durations (48 versus 24 hours), a metaanalytical summary of the BE RADIANT and BE SURE studies would not be appropriate. Instead, the studies were qualitatively summarized. For chronic diseases such as plaque psoriasis, longer study durations are preferable due to their longer follow-up duration, which helps assess the sustainability of effects. The BE RADIANT study, which is deemed to offer higher informative value due to its longer duration, was therefore used as the anchor for the qualitative summary. The assessment of extent as well as certainty of conclusions was initially based on the results of the BE RADIANT study, which has a higher informative value. The results of the study of higher informative value were not called into question by the BE SURE study. If the results of both studies have the same direction of effect and are statistically significant, the results of the BE SURE study can increase the certainty of conclusions of the BE RADIANT study. However, the fact that the available results offer different qualitative certainties of results is to be taken into account.

Due to the high risk of bias of the results of the morbidity and health-related quality of life outcomes, at most hints, e.g. of added benefit, can be derived from each of the 2 studies. Because of the uncertainties regarding the composition of the subpopulation for research question 1, it is not possible to upgrade from a hint to an indication on the basis of the overall analysis of both studies. Consequently, at most hints, e.g. of an added benefit, can be derived in the overall analysis of both studies for all relevant outcomes except overall survival and side effects. For all-cause mortality and side effects, at most indications, e.g. of an added benefit, can be derived.

Results

Mortality

Overall survival

No deaths had occurred in the BE SURE and BE RADIANT studies by Week 24 and 48, respectively. For all-cause mortality, this results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Remission (PASI 100)

The analysis of the studies showed a statistically significant effect in favour of bimekizumab for the outcome of remission, as measured with the PASI 100. However, this effect is smaller in the longer-duration BE RADIANT study than it is in BE SURE. This results in a hint of added benefit of bimekizumab in comparison with the ACT for the outcome of remission.

Absence of symptoms on the scalp (scalp IGA = 0)

At Week 24, the BE SURE study shows a statistically significant difference in favour of bimekizumab versus adalimumab for the outcome "absence of symptoms on the scalp (scalp IGA = 0)". However, there was no statistically significant difference between treatment arms in the determinative BE RADIANT study. Due to the lack of advantage in the determinative BE RADIANT study, this results in a hint of added benefit of bimekizumab in comparison with the ACT for this outcome; an added benefit is therefore not proven.

Absence of symptoms on palms and soles (ppIGA = 0) and absence of symptoms on fingernails (mNAPSI 100)

No usable data were available for the outcomes "absence of symptoms on palms and soles (ppIGA 0)" and "absence of symptoms on fingernails (mNAPSI 100)". For the outcomes "absence of symptoms on palms and soles (ppIGA = 0)" and "absence of symptoms on fingernails (mNAPSI 100)", this results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Patient-reported absence of symptoms

Psoriasis diary [PSD] itching, PSD pain

At Week 48, the BE RADIANT study showed a statistically significant difference in favour of bimekizumab versus secukinumab for the outcomes of PSD itching and PSD pain. This difference was no more than marginal, however. There was no statistically significant difference between the BE SURE treatment arms for either outcome. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

PSD scaling

At Week 48, the determinative BE RADIANT study showed a statistically significant difference between treatment arms in favour of bimekizumab versus secukinumab for the outcome of PSD scaling. However, no statistically significant difference between treatment arms was found in the BE SURE study. This results in a hint of added benefit of bimekizumab in comparison with the ACT.

PSD redness

For the outcome of PSD redness, no statistically significant difference between treatment arms was found in the BE SURE study. The outcome was not recorded in the BE RADIANT study. This resulted in no hint of added benefit of bimekizumab in comparison with adalimumab; an added benefit is therefore not proven.

PSD burning

For the outcome of PSD burning, no statistically significant difference between treatment arms was found in the BE SURE study. The outcome was not recorded in the BE RADIANT study.

This resulted in no hint of added benefit of bimekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Further patient-reported absence of symptoms (other scales of PSD)

Regarding further outcomes on patient-reported absence of symptoms (particularly cracking and bleeding), the company's dossier does not provide any data for the BE SURE study, and the outcomes were not surveyed in the BE RADIANT study. There was no hint of added benefit of bimekizumab in comparison with adalimumab for further outcomes on patient-reported absence of symptoms (particularly cracking and bleeding); an added benefit is therefore not proven.

Patient-reported symptoms (Patient Global Assessment)

The company presented no analyses on the outcome of Patient Global Assessment. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

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

For the outcome of health status, measured with EQ-5D VAS, the BE SURE study shows a statistically significant difference between treatment arms in favour of bimekizumab versus adalimumab. However, the 95% confidence interval (CI) of the standardized mean difference (SMD) (Hedges' g) was not completely outside the irrelevance range of -0.2 to 0.2. It can therefore not be inferred that the observed effect is relevant. No statistically significant difference between treatment arms was found for the determinative BE RADIANT study. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

DLQI ≤ 1

For the outcome of health-related quality of life, as measured with DLQI, the analysis shows a statistically significant difference between treatment arms in favour of bimekizumab versus adalimumab only for the BE SURE study. No statistically significant difference between treatment arms was found for the determinative BE RADIANT study. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Short Form-36 Health Survey [SF-36]

For the outcome of health-related quality of life, as measured with SF-36, the BE SURE study shows no statistically significant difference between treatment arms for either of the two summary scores (Physical Component Summary [PCS] or Mental Component Summary [MCS]). The outcome was not recorded in the BE RADIANT study. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, the determinative BE RADIANT study shows a statistically significant difference to the disadvantage of bimekizumab by Week 48. No SAEs occurred in the BE SURE study up to and including Week 24. This results in a hint of greater harm from bimekizumab in comparison with the ACT.

Discontinuation due to AEs and infections and infestations (SOC, AE)

Neither study showed any statistically significant difference between treatment arms for the outcomes of discontinuation due to adverse events (AEs) or infections and infestations (AE). This results in no hint of greater or lesser harm from bimekizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Fungal infectious disorders (HLGT, AE)

For the outcome of fungal infectious disorders (AE), both studies showed a statistically significant difference between treatment arms to the disadvantage of bimekizumab versus adalimumab or secukinumab. However, the extent of the effect was no more than marginal in both studies. This results in no hint of greater or lesser harm from bimekizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Research question 2: adult patients with inadequate response or intolerance to prior systemic therapy

Study pool and study design

As in research question 1, the BE SURE and BE RADIANT studies (see above) were used for the benefit assessment of bimekizumab in adult patients with moderate to severe plaque psoriasis with inadequate response or intolerance to prior systemic therapy (research question 2).

The design of the BE SURE and BE RADIANT studies is described under research question 1.

Subpopulation relevant for research question 2

Research question 2 of this benefit assessment comprises patients with moderate to severe plaque psoriasis with inadequate response or intolerance to prior systemic therapy. Consequently, only subpopulations of the BE SURE and the BE RADIANT studies were relevant for this research question. The company has formed these subpopulations by including patients who had received prior systemic psoriasis therapy and had discontinued it due to inadequate response and/or intolerance. Patients whose discontinuation of prior systemic therapy was due to other reasons were excluded.

The subpopulation used for research question 2 comprises 87 patients from the bimekizumab arm and 84 patients from the adalimumab arm of the BE SURE study and 128 patients from the bimekizumab arm and 228 patients from the secukinumab arm of the BE RADIANT study.

Risk of bias and certainty of conclusions

As already described for research question 1, the risk of bias at study level was rated as low for both BE SURE and BE RADIANT. For research question 2, the risk of bias for the results of the outcome of patient-reported absence of symptoms, surveyed using the PSD, is rated as high in the BE SURE study. According to the company's Module 4 B, up to and including Week 24, the patient population for research question 2 in the BE SURE study had only 1 study discontinuation due to lack of response per treatment arm. In the BE RADIANT study, 4 patients were documented as discontinuing the study early due to lack of response up to and including Week 48, all of whom were in the secukinumab arm. The results on the BE RADIANT outcomes of absence of symptoms on the scalp (scalp IGA = 0) and health status (EQ-5D VAS) are also rated as potentially highly biased. The risk of bias for the results of all other outcomes is rated as low in both studies.

As described under research question 1, no meta-analytical summary of the studies was carried out. Instead, a qualitative summary of the studies was conducted, using primarily the BE RADIANT study to derive added benefit; this study was therefore determinative regarding certainty of results and extent. On the basis of the available information, indications, e.g. of added benefit, can be derived from the BE RADIANT outcomes of all-cause mortality, remission (PASI 100), patient-reported absence of symptoms (PSD), health-related quality of life (DLQI ≤ 1), SAEs, discontinuation due to AEs, and all specific AEs. If the results of both studies have the same direction of effect and are statistically significant, the results of the BE SURE study can increase the certainty of conclusions of the BE RADIANT study in the overall analysis, so that proof can be derived for these outcomes.

Due to the high risk of bias, at most hints, e.g. of added benefit, can be derived for the BE RADIANT study's outcomes of absence of symptoms on the scalp (scalp IGA = 0) and health status (EQ-5D VAS), while from the BE SURE study, indications can be derived due to low risk of bias. If the results of both studies point in the same direction and are statistically significant, the certainty of the BE SURE study's results can be upgraded here as well, so that the overall analysis of both studies can derive indications for these outcomes. The outcome of health-related quality of life (SF-36) was surveyed only in the BE SURE study. The risk of bias for this outcome was low; therefore, an indication, e.g. of added benefit, can be derived for this outcome.

Results

Mortality

Overall survival

For the outcome of all-cause mortality, no statistically significant difference between treatment arms was found in the BE RADIANT study. No deaths occurred in the BE SURE study. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Remission (PASI 100)

For the outcome of remission, surveyed with the PASI 100, both studies showed a statistically significant difference between treatment arms. However, this difference is at most minor in the determinative BE RADIANT study. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Absence of symptoms on the scalp (scalp IGA = 0)

At Week 24, the BE SURE study shows a statistically significant difference in favour of bimekizumab versus adalimumab for the outcome of absence of symptoms on the scalp (scalp IGA = 0). However, no statistically significant difference between treatment arms was found for the determinative BE RADIANT study. Due to the lack of an advantage in the determinative BE RADIANT study, this results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Absence of symptoms on palms and soles (ppIGA = 0) and absence of symptoms on fingernails (mNAPSI 100)

No usable data were available for the outcomes of absence of symptoms on palms and soles (ppIGA 0) and absence of symptoms on fingernails (mNAPSI 100). This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Patient-reported absence of symptoms

PSD itching

For the outcome of PSD itching, the BE RADIANT study shows a statistically significant difference between treatment arms. This difference is no more than marginal, however. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

PSD pain

For the outcome of PSD pain, the BE RADIANT study shows no statistically significant difference between treatment arms. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

PSD scaling

For the outcome of PSD scaling, a statistically significant difference between treatment arms was found for both studies in favour of bimekizumab versus adalimumab or secukinumab. This results in proof of added benefit of bimekizumab in comparison with the ACT.

PSD redness

For the outcome of PSD redness, the BE SURE study shows a statistically significant difference between treatment arms in favour of bimekizumab versus adalimumab. The outcome was not

recorded in the BE RADIANT study. This results in a hint of an added benefit of bimekizumab in comparison with adalimumab.

PSD burning

For the outcome of PSD burning, the BE SURE study shows no statistically significant difference between treatment arms. The outcome was not recorded in the BE RADIANT study. This results in no hint of added benefit of bimekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Further patient-reported absence of symptoms (other PSD scales)

According to protocol, the BE SURE study surveyed further scales of patient-reported absence of symptoms. However, the company's dossier presents no data on this outcome for the relevant subpopulation. The BE RADIANT study did not survey any other scales of patient-reported absence of symptoms. This results in no hint of added benefit of bimekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Patient-reported symptoms (Patient Global Assessment)

According to the protocol, both studies surveyed the outcome of patient-reported symptoms (Patient Global Assessment). However, the company's dossier presents no data on this outcome for the relevant subpopulation. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

For the outcome of health status (EQ-5D VAS), no statistically significant difference between treatment arms was found for either study. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

DLQI ≤ 1

At Week 24, the BE SURE study showed a statistically significant difference in favour of bimekizumab versus adalimumab for the outcome of health-related quality of life, as measured with DLQI. However, no statistically significant difference between treatment arms was found for the determinative BE RADIANT study. Due to the lack of an advantage in the determinative BE RADIANT study, this results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

SF-36 PCS

For the outcome of health-related quality of life, surveyed with SF-36, the BE SURE study's PCS shows no statistically significant difference between treatment arms. The outcome was not recorded in the BE RADIANT study. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

SF-36 MCS

For the outcome of health-related quality of life, surveyed with SF-36, the BE SURE study's MCS shows a statistically significant difference between treatment arms. The CI for Hedges' g, however, is not completely outside the irrelevance range [-0.2; 0.2]. It can therefore not be inferred that the effect was relevant. The outcome was not recorded in the BE RADIANT study. This results in no hint of added benefit of bimekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs, and infections and infestations (SOC, AE)

Neither study showed any statistically significant difference between treatment arms for the outcomes of SAEs, discontinuation due to AEs, or infections and infestations (AEs). This results in no hint of greater or lesser harm from bimekizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Fungal infectious disorders (HLGT, AE)

For the outcome of fungal infectious disorders (AE), both studies show a statistically significant difference between treatment arms to the disadvantage of bimekizumab versus adalimumab or secukinumab. This results in proof of greater harm from bimekizumab in comparison with the ACT.

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

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

Research question 1: adult patients who are not candidates for conventional treatment in the framework of initial systemic therapy

The overall analysis shows both favourable effects in the outcome category of non-serious/non-severe symptoms / late complications and an unfavourable effect in the outcome category of serious/severe side effects. For each of the outcomes of remission PASI 100 and PSD scaling, there is a hint of minor added benefit of bimekizumab in comparison with adalimumab or secukinumab. For the outcome of SAEs, there is a hint of greater harm, but its extent is non-

[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].

quantifiable. This greater harm does not fully call into question the advantage in the outcomes of remission PASI 100 and PSD scaling.

In summary, for adult patients who are not candidates for conventional treatment in the framework of initial systemic therapy (research question 1), there is a hint of minor added benefit of bimekizumab in comparison with the ACT (adalimumab or secukinumab).

Research question 2: adult patients with inadequate response or intolerance to prior systemic therapy

The overall analysis shows both favourable effects in the outcome category of non-serious/non-severe symptoms / late complications and an unfavourable effect in the outcome category of non-serious/non-severe side effects. The outcomes of PSD scaling and PSD redness show proof and a hint, respectively, of minor added benefit of bimekizumab in comparison with adalimumab or secukinumab. By contrast, proof of greater harm of considerable extent was found for the outcome of fungal infectious disorders.

In summary, for patients with moderate to severe plaque psoriasis with inadequate response or intolerance to prior systemic therapy (research question 2), there is no hint of added benefit of bimekizumab in comparison with adalimumab or secukinumab; an added benefit is therefore not proven.

Table 3 shows a summary of the probability and extent of added benefit of bimekizumab.

Table 3: Bimekizumab – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
1	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**	Hint of minor added benefit
2	Adult patients with moderate to severe plaque psoriasis with inadequate response or intolerance to prior systemic therapy	**Adalimumab** or brodalumab or guselkumab or infliximab or ixekizumab or risankizumab or **secukinumab** or ustekinumab	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to 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 the derivation of 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 is to assess the added benefit of bimekizumab in comparison with the ACT in adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy.

The research questions shown in Table 4 result from the ACTs specified by the G-BA.

Table 4: Research questions of the benefit assessment of bimekizumab

Research question	Therapeutic indication	ACT[a]
1	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**
2	Adult patients with moderate to severe plaque psoriasis with inadequate response or intolerance to prior systemic therapy	**Adalimumab** or brodalumab or guselkumab or infliximab or ixekizumab or risankizumab or **secukinumab** or ustekinumab

a. Presented is the respective ACT specified by the GBA. In cases where the ACT specified by the G-BA allows the company to 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 ease of presentation and reading, the present benefit assessment uses the following designations for the research questions:

- Research question 1: adult patients who are not candidates for conventional treatment in the framework of initial systemic therapy
- Research question 2: adult patients with inadequate response or intolerance to prior systemic therapy

The company largely followed the G-BA's specification of the ACT for both research questions. In Module 3 A and Module 3 B, the company selected 2 drugs each (adalimumab and secukinumab) from the listed options. This methodology was not appropriate. Furthermore, the approach used in the company's dossier is inconsistent because, in its search for studies relevant for the assessment, the company appropriately included all drugs specified by the G-BA rather than limiting the inclusion criteria regarding the drugs used. Therefore, the company's pre-selection did not exclude any potentially relevant studies.

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 1: 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 bimekizumab (status: 2 July 2021)
- bibliographical literature search on bimekizumab (last search on 5 July 2021)
- search in trial registries / trial results databases for studies on bimekizumab (last search on 5 July 2021)
- search on the G-BA website for bimekizumab (last search on 2 July 2021)

To check the completeness of the study pool:

- search in trial registries for studies on bimekizumab (last search on 7 September 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

2.3.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
PS008 (BE SURE[c])	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6]
PS0015 (BE RADIANT[c])	No	Yes	No	Yes [7]	Yes [8,9]	Yes [10]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.

CSR: clinical study report; RCT: randomized controlled trial

2.3.1.2 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: bimekizumab vs. adalimumab or secukinumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
BE SURE	RCT, double-blind, parallel	▪ Adults (≥ 18 years) with chronic moderate to severe plaque psoriasis (PASI ≥ 12, BSA ≥ 10, IGA score ≥ 3) ▪ Diagnosis of disease at least 6 months before screening ▪ Candidates for systemic therapy and/or phototherapy	Bimekizumab Q4W[b] (N = 158) Bimekizumab Q4W/Q8W[c] (N = 161) Adalimumab/bimekizumab Q4W[d] (N = 159) Relevant subpopulations thereof[e]: ▪ Research question 1: Bimekizumab Q4W/Q8W (n = 45) Adalimumab/bimekizumab Q4W (n = 49) ▪ Research question 2: Bimekizumab Q4W/Q8W (n = 87) Adalimumab/bimekizumab Q4W (n = 84)	Screening: 2 to 5 weeks Treatment: ▪ Double-blind active-control initial phase: 16 weeks ▪ Dose-blinded maintenance phase[f]: 40 weeks Follow-up observation: Safety follow-up[g] 20 weeks after the last dose of study medication	77 centres in Australia, Canada, Germany, Hungary, Korea, Poland, Russia, Taiwan, USA 01/2018–02/2020 Data cut-offs: ▪ Interim analysis after 56 weeks of treatment: 28 October 2019 ▪ Final analysis after final visit on 26 February 2020	Primary: PASI 90 response at Week 16; IGA of 0 or 1 at Week 16 Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
BE RADIANT	RCT, double-blind, parallel	▪ Adults (≥ 18 years) with chronic moderate to severe plaque psoriasis (PASI ≥ 12, BSA ≥ 10, IGA score ≥ 3) ▪ Diagnosis of disease at least 6 months before screening ▪ Candidates for systemic therapy and/or phototherapy	Bimekizumab[h] (N = 373) ▪ From Week 16 Q4W[b] (N = 147) ▪ From Week 16 Q8W (N = 215) Secukinumab (N = 370) Relevant subpopulations thereof[e]: ▪ Research question 1: Bimekizumab Q4W/Q8W (n = 58) Secukinumab (n = 98) ▪ Research question 2: Bimekizumab Q4W/Q8W (n = 128) Secukinumab (n = 228)	Screening: 2 to 5 weeks Treatment: ▪ double-blind phase: 48 weeks ▪ optional open-label phase: 96 weeks Follow-up: safety follow-up[g] 20 weeks after the last dose of study medication	77 centres in Australia, Belgium, Canada, France, Germany, Great Britain, Netherlands, Poland, Spain, Turkey, United States 06/2018–ongoing Data cut-off: ▪ Interim analysis was after 48 weeks of treatment: 29 June 2020[i]	Primary: PASI 100 response at Week 16 Secondary: morbidity, health-related quality of life, AEs

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. The arm is not relevant for the assessment and is not presented in the following tables.
c. After 16 weeks, the dosing interval was switched from every 4 weeks to every 8 weeks. In the tables below, this treatment arm is referred to as "bimekizumab".
d. Adalimumab every 2 weeks up to Week 24, then switch to bimekizumab every 4 weeks. For this benefit assessment, adalimumab treatment up to Week 24 is relevant. In the tables below, this treatment arm is referred to as "adalimumab".
e. According to the company's Module 4, the subpopulations include, for research question 1, patients who are not candidates for conventional treatment in the framework of initial systemic therapy and, for research question 2, patients with inadequate response or intolerance to prior systemic therapy (see Sections 2.3.1.2 and 2.4.1.2. of this assessment for details on the composition of the subpopulations).
f. Afterwards, patients were eligible to switch to the open-label extension BE BRIGHT study.
g. For all patients who did not switch to the BE BRIGHT extension study or the open-label phase of the BE RADIANT study.
h. After 16 weeks, patients were re-randomized in a 1:2 ratio to bimekuzimab Q4W or Q8W.
i. Database lock for the interim report.

AE: adverse event; BSA: Body Surface Area; IGA: Investigator's Global Assessment; n: relevant subpopulation; N: number of randomized patients; PASI: Psoriasis Area and Severity Index; Q4W: every 4 weeks; Q8W: every 8 weeks; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab

Study	Intervention	Comparison
BE SURE	Active-control period (up to Week 24):	
	Bimekizumab s.c.	Adalimumab s.c.
	320 mg every 4 weeks up to and including Week 16 (initial phase), followed by every 8 weeks (maintenance phase)	80 mg at study start (Week 0), followed by 40 mg every 2 weeks starting 1 week after the initial dose
BE RADIANT	Bimekizumab s.c.	Secukinumab s.c.
	320 mg every 4 weeks up to and including Week 16 (initial phase), followed by every 8 weeks (maintenance phase)	300 mg at study start (Week 0), followed by weekly in Weeks 1, 2, 3, and 4, followed by every 4 weeks
	Treatment modifications ▪ No dose modifications were provided for; treatment discontinuation was largely in accordance with SPCs[a] [11-13]	
	Prohibited prior and concomitant treatment ▪ Experimental systemic psoriasis treatment (within 3 months or 5 half-lives before study start) or topical psoriasis treatment (within 1 month before start of study treatment) ▪ Topical therapies other than those allowed (within 2 weeks before study start) ▪ Systemic retinoids (within 3 months before study start) ▪ Non-biologic systemic therapy (immunosuppressants, fumaric acid esters for psoriasis treatment, systemic corticosteroids, phototherapy) within 1 month prior to study start ▪ TNF inhibitors (etanercept within 1 month, infliximab, golimumab, certolizumab pegol, and adalimumab within 3 months prior to study start [any prior exposure in BE SURE]) ▪ Other biologics and other systemic therapies (e.g. apremilast, tofacitinib - within 2 weeks of study start) ▪ anti-IL-17 therapy (brodalumab, ixekizumab, secukinumab within 3 months of study start [any prior exposure in BE RADIANT]) **Permitted concomitant treatment** ▪ Moisturisers or emollients, bath oils, oatmeal baths ▪ Mild topical corticosteroids for use on the face, armpits and/or genital area ▪ NSAIDs taken at a stable dose for at least 1 week before study start or mild analgesics (paracetamol or mild opioids) for the treatment of PsA ▪ i.a. steroids or hyaluronic acid (in BE SURE, only after Week 24).	

a. According to the SPCs of bimekizumab, secukinumab, and adalimumab, treatment discontinuation or modification should be contemplated in the absence of a response after 16 weeks of therapy. In departure from the SPC, both studies used only the following discontinuation criterion: from Week 28, patients who had been treated continuously for at least 12 weeks and consistently had IGA ≥ 3 were deemed nonresponders and were to discontinue therapy.

i.a.: intraarticular; IL: interleukin; IGA: Investigator's Global Assessment; NSAIDs: nonsteroidal antiinflammatory drugs; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis; RCT: randomized controlled trial; s. c.: subcutaneous; TNF: tumour necrosis factor

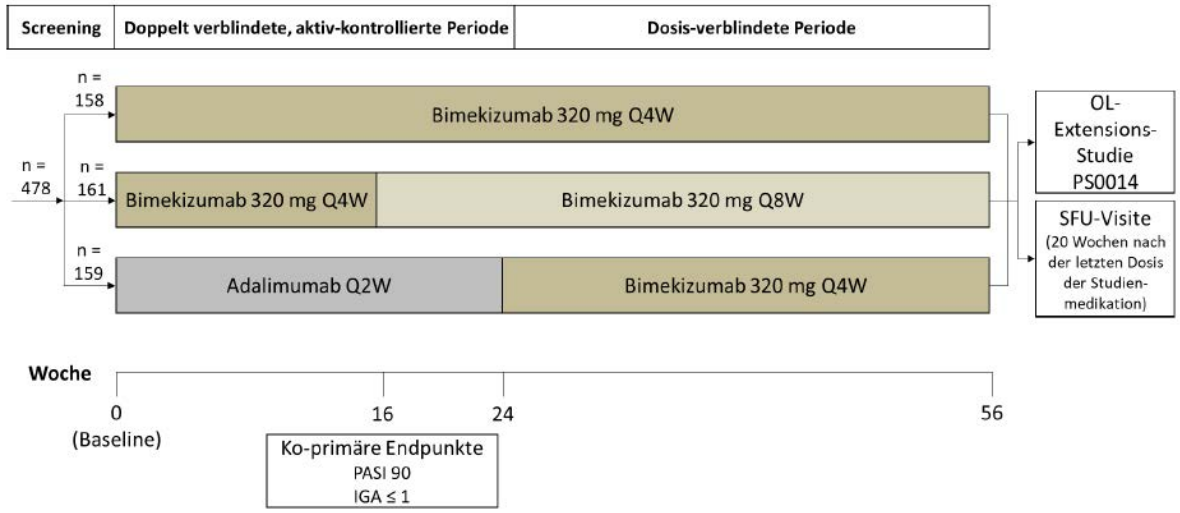
Study design

The BE SURE and BE RADIANT studies are randomized, active-control double-blind studies comparing 2 different dosing intervals of bimekizumab (Q4W = every 4 weeks and Q8W = every 8 weeks) with adalimumab (BE SURE) or secukinumab (BE RADIANT) in adults with

moderate to severe plaque psoriasis. In both studies, disease severity was defined using the following criteria: BSA ≥ 10%, PASI ≥ 12, and IGA ≥ 3 on a 5-point scale. For the present benefit assessment, this definition of the severity grade was deemed an adequate representation of moderate to severe psoriasis (see below).

The BE SURE study included a total of 478 patients and randomized them at a 1:1:1 ratio to treatment with bimekizumab every 4 weeks (Q4W) (N = 158), bimekizumab every 4 weeks followed by every 8 weeks (Q4W/Q8W) (N = 161), and adalimumab followed by bimekizumab Q4W (N = 159).

Figure 1 shows a diagram of the BE SURE study design.



Doppelt verblindete, aktiv-kontrollierte Periode = double-blind, active-control period; Dosis-verblindete Periode = dose-blinded period; OL-Extensionsstudie PS0014 = OL extension study PS0014; SFU-Visite (20 Wochen nach der letzten Dosis der Studienmedikation) = SFU visit (20 weeks after the last dose of study medication); Woche = Week; Ko-primäre Endpunkte = co-primary outcomes

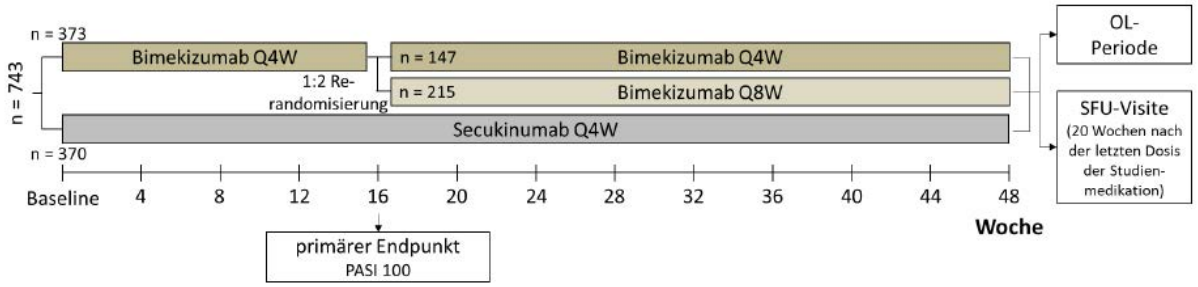
Figure 1: BE SURE study, schematic diagram of the study design

The study design comprised a (2-week to 5-week) screening phase, followed by a 24-week active-control treatment phase (last dose of adalimumab in Week 23), and then a dose-blinded phase up to and including Week 56 (last dose of bimekizumab in Week 48 or 52). In this dose-blinded phase (maintenance phase), patients in the adalimumab arm switched to bimekizumab Q4W. Subsequent to the maintenance phase, all patients were eligible for participating in an open-label extension study (BE BRIGHT). Patients who did not participate in the extension study or who prematurely discontinued the study medication had a follow-up visit 20 weeks after the last dose of the study medication. Due to the absence of a comparison with adalimumab, the dose-blinded phase (Week 24 through Week 56) is not relevant for the assessment and is therefore not considered further. Likewise, the bimekizumab Q4W arm was disregarded in the assessment due to the off-label continuous 4-week dosing [13].

For ease of reading, the adalimumab/bimekizumab/Q4W arm of the BE SURE study is referred to as "adalimumab" below. The bimekizumab Q4W/Q8W arm is designated as "bimekizumab".

The BE RADIANT study included a total of 743 patients who were randomly assigned at a 1:1 ratio to treatment with bimekizumab Q4W (N = 373) or secukinumab Q4W (N = 370).

Figure 2 graphically presents the BE RADIANT study design.



1:2 Rerandomisierung = 1:2 rerandomization; OL-Periode = OL period; SFU-Visite (20 Wochen nach der letzten Dosis der Studienmedikation) = SFU visit (20 weeks after the last dose of study medication); primärer Endpunkt = primary outcome; Woche = Week

Figure 2: BE RADIANT study, schematic diagram of the study design

The design of the study comprises a (2-week to 5-week) screening phase followed by a 48-week active-control, double-blind treatment phase (last dose of study medication in Week 44). After the first 16 treatment weeks, the bimekizumab Q4W arm was split up, and patients were randomized at a 1:2 ratio to treatment with bimekizumab every 4 weeks (Q4W, N = 147) or every 8 weeks (Q4W/Q8W, N = 215). After completing the blinded treatment phase, patients were eligible to participate in a 96-week open-label phase. Irrespective of their participation in the open-label phase, all patients were to have a follow-up visit 20 weeks after the last dose of the study medication. At the present data cut-off point, all patients had completed the visit at Week 48. The present assessment is based on the data from the active-control treatment phase. As in the BE SURE study, the bimekizumab Q4W arm was disregarded because of its dosing being off-label [13].

For ease of reading, the BE RADIANT study's bimekizumab Q4W/Q8W arm, which is dosed as approved, is referred to as "bimekizumab", and the secukinumab Q4W arm, as "secukinumab".

Both studies were stratified by region (North America, Western Europe, Central and Eastern Europe, Asia and Australia) and prior biologic therapy (yes versus no).

The co-primary outcomes of the BE SURE study are PASI 90 and IGA score 0 or 1 with simultaneous improvement by at least 2 scale points from baseline to Week 16. Patient-relevant

secondary outcomes are remission (PASI 100) at Week 24 as well as outcomes on symptoms, health-related quality of life, and side effects.

The primary outcome of the BE RADIANT study is remission (PASI 100) at Week 16. Patient-relevant secondary outcomes are remission (PASI 100 at Week 48) as well as outcomes on symptoms, health-related quality of life, and side effects.

Data cut-offs

Two data cut-offs are available for the BE SURE study:

- Data cut-off 28 October 2019: prespecified interim analysis after a total of 56 weeks of treatment (16-week initial phase + 40-week maintenance phase)
- Data cut-off 26 February 2020 (date of last visit): final analysis after the last patient's final visit, including follow-up visit 20 weeks after the last dose of the study medication

In its dossier, the company presents analyses of the data after 24 weeks of treatment based on the 1st data cut-off of 28 October 2019.

For the BE RADIANT study, 1 data cut-off is available:

- Data cut-off 29 June 2020: prespecified interim analysis after a total of 48 weeks of treatment (16-week initial phase + 32-week maintenance phase)

In its dossier, the company presents analyses of the data after 48 weeks of treatment based on the data cut-off of 29 June 2020.

Treatment departs from SPC

Treatment in both studies was largely in compliance with the SPCs, both in the bimekizumab arms and in the adalimumab/secukinumab arm [11-13]. The following aspects should be noted but remain without consequence for the benefit assessment:

- In both bimekizumab arms, BE SURE study participants were to initially receive a bimekizumab dose every 4 weeks, up to and including Week 16. After Week 16, the 4-weekly dosing interval was to be continued in the Q4W arm. Since this dosing regimen departs from the SPC, this treatment arm is not relevant for the present benefit assessment. In the Q4W/Q8W arm, in contrast, the bimekizumab dose was switched from a 4-week interval to an 8-week interval as specified by the SPC. In the Q4W/Q8W arm, blinding was ensured by additional placebo injections at Weeks 20, 28, 36, 44, and 52. In departure from the SPC, however, 24 of the 161 patients in the bimekizumab Q4W/Q8W arm (15%) received another dose of bimekizumab instead of placebo in Week 20. In Module 4 A, the company reports that sensitivity analyses excluding the patients in question for the secondary outcomes of PASI 90, PASI 100, and IGA response at Week 24 show that the erroneous dosing did not affect the overall conclusion.

- For patients not responding to treatment after 16 weeks, the SPCs of bimekizumab, adalimumab, and secukinumab specify either giving consideration to or carefully considering treatment discontinuation. In this regard, both studies' documents specify merely that treatment discontinuation was to be considered due to non-response (IGA ≥ 3 consistently for at least 4 weeks) at Week 28. According to the company's Modules 4 A and 4 B, no study discontinuation due to non-response was recorded for the subpopulations in research question 1. The subpopulation for research question 2 exhibited 1 study discontinuation due to non-response in the BE SURE study and 4 in the BE RADIANT secukinumab arm (see Sections 2.3.2.2 and 2.4.2.2, respectively). Nevertheless, it remains unclear whether additional patients exhibited non-response to treatment by Week 16.
- According to the adalimumab SPC, patients treated with 40 mg adalimumab who exhibit insufficient response at Week 16 may benefit from a dose increase every 2 weeks (40 mg every week or 80 mg every other week). The BE SURE study did not provide for this individualized dose modification; the company's dossier deems this difference to be irrelevant for the results because there were no study discontinuations due to non-response.
- According to the bimekizumab SPC, some patients with a body weight ≥ 120 kg who did not achieve complete skin clearance at Week 16 may exhibit improved response on a 4-weekly dosing interval. This was not addressed by the company in the study documents or in the dossier. The available documents also do not show to how many patients this applies. The vast majority of patients in both studies had a body weight under 100 kg.

The above-mentioned deviations presumably did not influence the study results in a relevant way.

Studies' definition of severity of disease

No uniform definition of the severity of plaque psoriasis generally exists. For example, the EMA deems PASI > 10 or BSA > 10% a suitable operationalization of moderate to severe plaque psoriasis [14]. The 2011 European consensus defines moderate to severe plaque psoriasis as "BSA > 10 or PASI > 10) and DLQI > 10" [15]. In addition to the 2011 definition, the 2020 EuroGuiDerm guideline [16] offers several definitions without specific thresholds. The German S3 guideline [17], on which the EuroGuiDerm guideline is based, defines moderate to severe psoriasis in accordance with the European consensus, namely as "(BSA > 10 or PASI > 10) and DLQI > 10". In addition, the guideline specifies "upgrade criteria" in the presence of which psoriasis is classified as moderate to severe, irrespective of the above criteria. These criteria include, among others, infestation of visible body regions or of the scalp, palms of the hands and soles of the feet, and onycholysis or onychodystrophy on at least 2 fingernails [17].

The BE SURE and BE RADIANT studies defined moderate to severe plaque psoriasis as PASI ≥ 12 and BSA ≥ 10 and IGA ≥ 3. The DLQI as another potential criterion for the severity

of plaque psoriasis was not an inclusion criterion for the BE SURE and BE RADIANT studies. In both studies, the mean DLQI at baseline was between 8 and 10 and hence slightly below the threshold specified by the S3 guideline. However, both studies' populations included a large percentage of patients with involvement of the fingernails, palms, and soles as well as the scalp.

In this light, while the severity definition used by the company disregarded the DLQI, it nevertheless adequately represented moderate to severe plaque psoriasis for the purposes of the present benefit assessment. With regard to PASI, the studies did not investigate patients with PASI scores between 10 and 12, who can also exhibit moderate to severe plaque psoriasis.

Subpopulation relevant for research question 1

Both studies included patients who the investigator deemed to be candidates for systemic therapy and/or phototherapy and for whom treatment with the respective ACT (adalimumab or secukinumab) was suitable according to the local SPC. The populations of both studies were therefore more inclusive than the population of this assessment's research question 1 (patients who are not candidates for conventional treatment in the framework of initial systemic therapy). Therefore, the company presented the results of a subpopulation in each case.

For research question 1, the company included only BE SURE and BE RADIANT participants who had not received any systemic psoriasis therapy prior to enrolment and who, according to the company, were not candidates for conventional treatment.

In accordance with the German S3 guideline, unsuitability of conventional systemic therapy stems from factors in the presence of which adequate treatment success of conventional systemic therapy is not to be expected. These criteria include, among others, particularly severe psoriasis (e.g. PASI ≥ 20) or particularly severe reduction of quality of life (e.g. DLQI ≥ 15) or severe involvement of the fingernails or scalp [17]. Since the physician's assessment also takes into account individual criteria, the G-BA recommended documenting the clinical criteria if a decision is made in favour of initial systemic therapy with nonconventional therapy based on individual criteria upon the physician's discretion. The company's dossier provides no further specific criteria to define unsuitability of conventional systemic therapy. The company's dossier lists only the patient population's high overall disease burden as sufficient justification for inclusion in research question 1.

Even based on the patient characteristics of the subpopulations formed by the company, it is impossible to determine whether all patients of the subpopulation were, in fact, not candidates for conventional therapy. In both studies, the median PASI score was about 17, with only 20–30% of patients exhibiting a PASI score ≥ 20 (see Table 8). Both studies included patients with nail psoriasis, scalp, palm, and sole involvement at enrolment. The majority of patients (> 90%) had scalp involvement, while only about half had nail psoriasis, and less than one-third exhibited palm and sole involvement. The mean DLQI was 8 to 10 in both studies.

In summary, the company's aggregated data do not clarify whether each individual patient actually qualified for inclusion in the subpopulation for research question 1 and which specific criteria led to the selection in each case. No information is available on the physician's individual considerations and evaluations regarding the treatment decision in each case. However, these problems did not lead to exclusion of the studies from research question 1. Rather, drawing conclusions on the added benefit of bimekizumab in comparison with the ACT was deemed possible on the basis of the results of the studies. Nevertheless, the uncertainties described were taken into account in the assessment of the certainty of conclusions (see Section 2.3.2.2).

For both studies, the subpopulations used to answer research question 1 included about one-third of the patients originally randomized to the study arms. In total, 45 patients in the bimekizumab arm and 49 patients in the adalimumab arm of the BE SURE study met the company's inclusion criteria for research question 1. For the BE RADIANT study, the same applied to 58 patients in the bimekizumab arm and 98 patients in the secukinumab arm.

Table 8 shows the patient characteristics for the included studies.

Table 8: Characteristics of the study populations – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab (research question 1: initial systemic therapy) (multipage table)

Study	BE SURE		BE RADIANT	
Characteristic Category	Bimekizumab	Adalimumab	Bimekizumab	Secukinumab
	N[a] = 45	N[a] = 49	N[a] = 58	N[a] = 98
Age [years], mean (SD)	42 (14)	46 (15)	45 (15)	43 (15)
Sex [f/m], %	20/80	35/65	26/74	36/64
Body weight [kg], mean (SD)	92.6 (21.7)	94.5 (26.0)	93.3 (21.5)	89.3 (20.4)
Weight [kg], n (%)				
≤ 100	30 (67)	32 (65)	40 (69)	74 (76)
> 100	15 (33)	17 (35)	18 (31)	24 (24)
Ancestry, n (%)				
White	36 (80)	43 (88)	55 (95)	92 (94)
Asian	7 (16)	2 (4)	0 (0)	3 (3)
Other	2 (4)[b]	4 (8)[b]	3 (5)[c]	3 (3)[c]
Region, n (%)				
North America	35 (78)	33 (67)	24 (41)	53 (54)
Western Europe	1 (2)	1 (2)	3 (5)	18 (18)
Central and Eastern Europe	7 (16)	13 (27)	22 (38)	21 (21)
Asia and Australia	2 (4)	2 (4)	9 (16)	6 (6)
PASI, mean (SD)	18.4 (5.4)	18.7 (5.9)	17.5 (4.3)	18.1 (5.3)
PASI, median [min; max]	17.1 [12.0; 36.5]	16.3 [12.0; 35.8]	16.9 [7.9; 29.7]	17.4 [12.0; 35.7]
PASI, n (%)				
< 20	31 (69)	34 (69)	46 (79)	71 (72)
≥ 20	14 (31)	15 (31)	12 (21)	27 (28)
Fingernail involvement (mNAPSI >0), n (%)				
Yes	29 (64)	24 (49)	29 (50)	41 (42)
No	16 (36)	25 (51)	29 (50)	57 (58)
Fingernail involvement (mNAPSI), mean (SD)[d]	12.4 (10.7)	13.8 (10.9)	17.9 (13.7)	20.2 (24.5)
Scalp involvement (scalp IGA grade), n (%)				
0 (clear)	1 (2)	6 (12)	4 (7)	5 (5)
1 (almost clear)	1 (2)	3 (6)	0 (0)	4 (4)
2 (mild)	13 (29)	12 (24)	10 (17)	20 (20)
3 (moderate)	21 (47)	22 (45)	36 (62)	56 (57)
4 (severe)	9 (20)	6 (12)	8 (14)	13 (13)

Table 8: Characteristics of the study populations – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab (research question 1: initial systemic therapy) (multipage table)

Study	BE SURE		BE RADIANT	
Characteristic Category	Bimekizumab	Adalimumab	Bimekizumab	Secukinumab
	N[a] = 45	N[a] = 49	N[a] = 58	N[a] = 98
Palm and sole involvement (ppIGA grade), n (%)				
0 (clear)	29 (64)	35 (71)	40 (69)	79 (81)
1 (almost clear)	5 (11)	6 (12)	5 (9)	2 (2)
2 (mild)	6 (13)	5 (10)	7 (12)	3 (3)
3 (moderate)	5 (11)	1 (2)	4 (7)	11 (11)
4 (severe)	0 (0)	2 (4)	2 (3)	3 (3)
Psoriatic arthritis (PGADA > 0)				
Yes	38 (84)	42 (86)	40 (69)	56 (57)
No	7 (16)	7 (14)	18 (31)	42 (43)
DLQI, mean (SD)	10.1 (6.2)	9.4 (7.6)	8.5 (6.1)	10.2 (6.3)
Diagnosis of disease [years ago], mean (SD)	13.5 (10.0)	11.9 (10.7)	13.2 (11.5)	13.1 (11.3)
Severity (IGA grade), n (%)[e]				
2 (mild)	0 (0)	0 (0)	2 (3)	0 (0)
3 (moderate)	32 (71)	35 (71)	43 (74)	71 (72)
4 (severe)	13 (29)	14 (29)	13 (22)	27 (28)
Treatment discontinuation, n (%)	ND	ND	ND	ND
Study discontinuation, n (%)[f]	3 (7)	6 (12)	2 (3)	17 (17)

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. Including Black/Other/Mixed; IQWiG calculation.
c. Including Black/ Native American or Alaska Native / Native Hawaiian and Other Pacific Islander; IQWiG calculation.
d. Only patients who had fingernail involvement at baseline.
e. According to both studies' inclusion criteria, only patients with IGA ≥ 3 were to be included.
f. No deaths occurred in either study.

f: female; IGA: Investigator's Global Assessment; m: male; max: maximum; min: minimum; mNAPSI: modified Nail Psoriasis Severity Index; n: number of patients in the category; N: number of randomized patients; ND: no data; PASI: Psoriasis Area and Severity Index; PGADA: Patient Global Assessment of Disease Activity; ppIGA: palmoplantar IGA; RCT: randomized controlled trial; SD: standard deviation

In view of the relatively small case numbers, the subpopulations' patient characteristics are largely comparable, both between the studies and between treatment arms. This applies to both demographic and disease characteristics. The mean age of the participants in both studies was about 44 years; most of them were male and white. However, the percentage of male patients of Asian ancestry was slightly higher in the bimekizumab arm than in the adalimumab arm of the BE SURE study. In both the BE SURE study's adalimumab arm and the BE RADIANT study's bimekizumab arm, almost twice as many patients were from Central and Eastern Europe compared to the respective other treatment arm.

Regarding disease characteristics, there were differences in the proportions of patients with known psoriatic arthritis. The percentage was higher in the BE RADIANT study's bimekizumab arm than in the secukinumab arm. The mean PASI score was 18 to 19, with about 20% to 30% of patients having a PASI score of ≥ 20.

Patients had been diagnosed with the disease an average of about 13 years ago. Both studies included patients with nail psoriasis, scalp, palm, and sole involvement at enrolment. The majority of patients (> 90%) had scalp involvement, while about half had nail psoriasis and less than one-third had palm and sole involvement.

The percentage of study drop-outs in the bimekizumab arm was 7% for the BE SURE study and 2% for the BE RADIANT study, compared to 12% each in the adalimumab and secukinumab arms. The company did not report the number of patients from the relevant subpopulation who discontinued therapy.

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: bimekizumab vs. adalimumab or secukinumab

Study	Adequate random sequence generation	Allocation concealment	Blinding		Non-selective reporting	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
BE SURE	Yes	Yes	Yes	Yes	Yes	No	Low
BE RADIANT	Yes	Yes	Yes	Yes	Yes	No	Low
RCT: randomized controlled trial							

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

Transferability of the study results to the German health care context

The company finds that the results of the BE SURE and BE RADIANT studies are transferable to the German health care context. It bases this assertion on the following reasoning:

The severity of disease according to the European consensus, on which the German S3 guideline is based as well, is reportedly moderate to severe (PASI > 10 or BSA > 10; DLQI > 10) in both studies. Comparing the study populations' characteristics with those of the

German psoriasis registry PsoBest and the Swiss registry Swiss Dermatology Network for Targeted Therapies [18], the company describes the study population and the target population as being comparable with regard to common patient characteristics (age, weight, sex, comorbidities, and disease duration).

The company further argues that the therapy recommendation issued in the German S3 guideline also provides for treatment with a biologic for study participants based on the defined inclusion criteria. The studies' exclusion criteria reportedly take into account the contraindications of the drugs listed as ACTs. The study dosages of bimekizumab and the drugs of the ACT reportedly correspond to the dosages approved in Germany. The company states that to assess effectiveness, the patient-relevant outcomes surveyed in routine clinical practice for evaluating treatment response upon recommendation by the German S3 guidelines were recorded as well.

It did not provide any further information, not even for the relevant subpopulations, regarding the transferability of the study results to the German health care context.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - All-cause mortality
- Morbidity
  - Remission (PASI 100)
  - Absence of symptoms on the scalp (scalp IGA 0)
  - Absence of symptoms on palms and soles (palmoplantar [pp]IGA 0)
  - Absence of symptoms on fingernails (mNAPSI 100)
  - Patient-reported absence of symptoms Patient Symptom Diary (PSD)
  - Patient-reported symptoms Patient Global Assessment
  - Health status (EQ-5D VAS)
- Health-related quality of life
  - DLQI ≤ 1
  - SF-36 version 2 (SF-36v2)
- Side effects
  - SAEs
  - Discontinuation due to AEs

- Infections and infestations (SOC)
- Fungal infectious disorders (High-Level Group Term [HLGT])

Qualitative summary of results

Despite different drugs being used in the comparator arms, a summary analysis of the two studies is generally possible because the drugs of the ACT are deemed equivalent. Treatment durations differ, however. For the BE RADIANT study, results are available for Week 32 and Week 48, whereas for the BE SURE study, only the results at Week 24 are relevant because of the switch from adalimumab to bimekizumab. The present benefit assessment uses the BE SURE analyses at Week 24 and the BE RADIANT analyses at Week 48. Due to the difference in follow-up periods, it is not appropriate to carry out a metaanalysis of the BE RADIANT results for Week 32 or Week 48 and BE SURE results at Week 24. Instead, the studies were qualitatively summarized. The PASI results of the BE RADIANT study at Week 32 are presented as supplementary information in Appendix B of the full dossier assessment.

For chronic diseases such as plaque psoriasis, longer study durations are preferable due to their longer follow-up duration, which helps assess the sustainability of effects. Therefore, the BE RADIANT study, which is deemed to be of higher informative value due to its longer study duration, is used as the anchor for the qualitative summary. The assessment of extent as well as certainty of conclusions was initially based on the results of the BE RADIANT study, which has a higher informative value. The results of the study of higher informative value were not called into question by the BE SURE study. If the results of both studies are statistically significant and have the same direction of effects, the results of the BE SURE study can increase the certainty of conclusions of the BE RADIANT study, provided no other aspects reduce the certainty or results. In the present research question, however, higher-level uncertainties were found with regard to the subpopulation submitted by the company on research question 1 (see Section 2.3.1.2). It remains uncertain whether conventional systemic therapy was in fact unsuitable for all patients in the subpopulation used to answer research question 1. This issue has been taken into account in the derivation of certainty of conclusions (see Section 2.3.2.2). For the determination of extent, the BE RADIANT study result was used due to its longer follow-up period.

Selection of relevant operationalizations

For the outcomes it used, the company submitted different analyses in some cases (e.g. responder analyses with different thresholds, time-to-event analyses, and changes over the course of the study). In the present benefit assessment, analyses on the percentage of patients with an event by Week 24 or Week 48 were used for the outcomes of remission (PASI 100), absence of symptoms on fingernails (mNAPSI 100), absence of symptoms on the scalp (scalp IGA = 0) and on the palms and soles (ppIGA = 0), patient-reported absence of symptoms (PSD items = 0) as well as DLQI (0 or 1). For the morbidity outcome of health status, measured with EQ-5D, and health-related quality of life, measured with SF-36, analyses of mean change from

the mixed-effects model repeated measures (MMRM) were used. Analyses of the proportion of patients with an event up to Week 24 or Week 48 were used for the outcomes of all-cause mortality, SAEs, discontinuation due to AEs, infections and infestations (SOC), and fungal infectious disorders (HLGT).

The choice of patient-relevant outcomes differs from the selection by the company, whose dossier (Module 4 A) (a) submitted no data for the outcome of Patient Global Assessment and (b) used additional outcomes.

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

Table 10: Matrix of outcomes – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab (research question 1: initial systemic therapy)

Study	Outcomes													
	All-cause mortality	Remission (PASI 100[a])	Patient-reported absence of symptoms (PSD[b])	Patient-reported symptoms (Patient Global Assessment)	Absence of symptoms on the scalp (scalp IGA[c])	Absence of symptoms on palms and soles (ppIGA[c])	Absence of symptoms on fingernails (mNAPSI 100[a])	Health status (EQ-5D VAS)	Health-related quality of life (DLQI[d])	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Infections and infestations (SOC, AEs)	Fungal infectious disorders (HLGT, AE)[e]
BE SURE	Yes	Yes	Yes	No[f]	Yes	No[g]	No[g]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
BE RADIANT	Yes	Yes	Yes	No[f]	Yes	No[g]	No[g]	Yes	Yes	No[h]	Yes	Yes	Yes	Yes

a. Score improvement by 100% from baseline.
b. Operationalized as domain score = 0. The BE SURE study surveyed 14 domains, but the company presents data only on the domains of itching, pain, scaling, redness, and burning; the BE RADIANT study surveyed only the 3 domains of itching, pain, and scaling.
c. Operationalized as scalp IGA or ppIGA = 0.
d. Operationalized as DLQI ≤ 1.
e. HLGT "fungal infectious disorders"; the events are largely based on the PT of "oral candidiasis".
f. No data available; for the reasoning, see this dossier assessment's text below.
g. No usable data available; for reasoning, see this dossier assessment's text below.
h. Outcome not recorded.

AE: adverse event; DLQI: Dermatology Life Quality Index; HLGT: high level group term; IGA: Investigator's Global Assessment; mNAPSI: modified Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index; pp: palmoplantar; PSD: psoriasis diary; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form 36-Item Health Survey; SOC: system organ class; VAS: visual analogue scale

Not for all outcomes listed in Table 10 did the company's dossier contain usable data. This is explained below.

Selection of relevant analyses for morbidity and health-related quality of life

Plaque psoriasis is a chronic disease with fluctuating severity of symptoms. Operationalizations which take into account the timing of the change in symptoms (e.g. measured as area under the curve) would more adequately reflect the course of disease than time-to-event analyses or analyses at a certain time point (e.g. at Week 24 or 48). Time-to-event analyses take into account only the 1st event for each symptom, without regard to its further course. Analyses at the end of the study, in contrast, do not allow drawing a conclusion as to whether the effect observed at that time remained stable over the course of the study. However, the available curves over time (see Appendix C of the full dossier assessment) suggest that the effects remain stable throughout the study. Consequently, the responder analyses can be used for assessing the outcomes.

Morbidity – patient-reported absence of symptoms (PSD itching, PSD pain, PSD scaling, PSD redness, PSD burning)

The company presents its internally developed electronic diary as a tool for recording patient-relevant psoriasis symptoms. The diary comprises 14 domains to take into account the different aspects of the disease and their effect on patients' quality of life: itching, pain, scaling, redness, burning, cracking, dryness, irritation, sensitivity, lesions, thickening, fatigue, embarrassment, and clothing choice. The BE SURE study surveyed all 14 domains daily. The company's dossier, however, presented results for only 5 domains (itching, pain, scaling, redness, burning). The BE RADIANT study, in contrast, surveyed only 3 of the 14 domains (itching, pain, scaling), initially every 4 weeks and subsequently every 16 weeks; the results are presented in the dossier. Consequently, data are missing on important psoriasis symptoms, particularly on cracking and bleeding (in the BE RADIANT study, additionally redness and burning). The company's selective choice and presentation or selective survey of outcomes is therefore not appropriate.

Nevertheless, the present benefit assessment includes the cited individual items as separate outcomes based on their face validity. This concurs with the company's approach. In addition, it should be noted that sufficiently validated instruments for the complete survey of psoriasis symptoms already exist; they include the Psoriasis Symptom and Sign Diary (PSSD) [19] and the Psoriasis Symptom Inventory (PSI) [20].

Morbidity – patient-reported symptoms (Patient Global Assessment)

Both studies surveyed the patient-relevant outcome of Patient Global Assessment as part of the diary. However, Module 4 A of the company's dossier did not present any data on this outcome.

Morbidity – absence of symptoms on the scalp, fingernails, palms, soles (scalp IGA, mNAPSI 100 and ppIGA)

In the analysis of scalp IGA, response was originally defined as the achievement of grade 0 (clear) or 1 (almost clear). For the dossier, the company has presented a post-hoc analysis which defines response as the achievement of scalp IGA grade 0 with simultaneous improvement by at least 2 points. This operationalization is suitable for the benefit assessment since absence of symptoms on the scalp (IGA = 0) is deemed patient relevant.

The analysis of the percentage of patients with absence of symptoms on the scalp (scalp IGA = 0) included only patients who had at least grade 2 psoriasis symptoms on the scalp at baseline (scalp IGA ≥ 2). While an analysis on the basis of all randomized patients would have been necessary, this operationalization includes about 89% of randomized patients relevant for research question 1 from the BE SURE study and 92% of said patients from the BE RADIANT study. Therefore, the analysis included the results from a sufficiently high percentage of randomized patients (> 80%). Hence, the outcome is suitable for the present assessment.

The analysis of the percentage of patients with mNAPSI 100 included results only from patients who already had fingernail psoriasis at baseline (mNAPSI > 0). This operationalization includes only about 57% or 46%, respectively, of randomized patients relevant for research question 1 from the BE SURE and BE RADIANT studies, thereby excluding a substantial portion of the study population. Additionally, this analysis excludes patients who experience initial or worsening symptoms.

The analysis of the percentage of patients with ppIGA = 0 also was restricted to patients who already had at least grade 2 psoriasis of the palms or feet (ppIGA ≥ 2) at baseline. Only about 20% each of the randomized patients relevant for research question 1 were taken into account for both studies; a substantial proportion of the study population was excluded from the analysis. In addition, this analysis disregards patients with psoriasis rated as almost clear (ppIGA = 1) as well as patients with initial or worsening symptoms.

For the outcomes of absence of symptoms on palms and soles and absence of symptoms on fingernails, an analysis on the basis of all randomized patients would have been necessary as well. However, these analyses were not available. Due to the insufficient percentage of patients included in the analysis, the results for these outcomes are unusable. The analyses presented by the company for mNAPSI 100 and ppIGA were therefore disregarded for the present benefit assessment. See the supplementary information provided in Appendix B of the full dossier assessment for the results on mNAPSI100 and ppIGA.

2.3.2.2 Risk of bias

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

Table 11: Risk of bias at study and outcome levels – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab (research question 1: initial systemic therapy)

Study		Outcomes													
	Study level	All-cause mortality	Remission (PASI 100[a])	Patient-reported absence of symptoms (PSD[b])	Patient-reported symptoms (Patient Global Assessment)	Absence of symptoms on the scalp (scalp IGA[c])	Absence of symptoms on palms and soles (ppIGA[c])	Absence of symptoms on fingernails (mNAPSI 100[a])	Health-related quality of life (DLQI[d])	Health-related quality of life (SF-36)	Health status (EQ-5D VAS)	SAEs	Discontinuation due to AEs	Infections and infestations (SOC, AEs)	Fungal infectious disorders (HLGT, AE)[e]
BE SURE	L	L	H[f]	H[f]	–[g]	H[f,h]	–[i]	–[i]	H[f]	H[j]	H[j]	L	L	L	L
BE RADIANT	L	L	H[f]	H[f]	–[g]	H[f]	–[i]	–[i]	H[f]	–[k]	H[h,j]	L	L	L	L

a. Score improvement by 100% from baseline.
b. Operationalized as domain score = 0. The BE SURE study surveyed 14 domains, but the company presents data only on the domains of itching, pain, scaling, redness and burning. The BE RADIANT study surveyed only the 3 domains of itching, pain, and scaling.
c. Operationalized as scalp IGA or ppIGA = 0.
d. Operationalized as DLQI ≤ 1.
e. HLGT "fungal infectious disorders"; the events are largely based on the PT of "oral candidiasis".
f. High and differing percentages of NRI-replaced values; see Table 12.
g. No usable data available; for reasons, see Section 2.3.2.1 of the present dossier assessment.
h. Missing values in analysis > 10%; see Table 12.
i. No usable data available; for a discussion, see Section 2.3.2.1 of the present dossier assessment.
j. Difference in the percentage of missing values between study arms: > 5%; see Table 12.
k. Outcome not recorded.

AE: adverse event; DLQI: Dermatology Life Quality Index; H: high: HLGT: high level group term; IGA: Investigator's Global Assessment; L: low; mNAPSI: modified Nail Psoriasis Severity Index; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; pp: palmoplantar; PSD: psoriasis diary; PT: preferred term; RCT: randomized controlled trial; SF-36: Short Form 36-Item Health Survey; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

The risk of bias was rated high for the results on all outcomes except all-cause mortality and the side effects outcomes (SAEs, discontinuation due to AEs, infections and infestations [SOC] as well as fungal infectious disorders [HLGT]). This is due to the high and differing percentages of patients whose results were, in part, replaced using non-responder imputation (NRI) (see Table 12). NRI rates patients with missing values as non-responders. However, values might be missing for reasons other than non-response. The company's Module 4 A, at least, showed no study discontinuation due to lack of response for research question 1, neither in BE SURE (Week 24) nor in BE RADIANT (Week 48).

For the outcome of health status, as measured with EQ-5D VAS, the high risk of bias also results from a high percentage of missing patients in the BE RADIANT secukinumab arm.

No data on outcomes regarding further patient-reported absence of symptoms (particularly cracking and bleeding) are available for either study.

No usable data are available for the outcomes of absence of symptoms on palms and soles (ppIGA = 0) and absence of symptoms on fingernails (mNAPSI 100) because all analyses included only patients with baseline mNAPSI 0 or ppIGA ≥ 2.

The sensitivity analyses presented by the company's Module 4 A (observed case analyses [BE SURE, BE RADIANT], multiple imputation [BE RADIANT]) are unsuitable for increasing the certainty of conclusions for the outcomes on symptoms and health-related quality of life because they take into account only patients with certain baseline scores or because the percentage of missing values is too high and differs between arms.

Table 12: Overview of replaced values in individual outcomes of the BE SURE and BE RADIANT studies for evaluating the risk of bias on the outcome level (research question 1: initial systemic therapy)

Outcome Time point (replacement strategy)	BE SURE		BE RADIANT	
	Bimekizumab (N = 45)	Adalimumab (N = 49)	Bimekizumab (N = 58)	Secukinumab (N = 98)
Study drop-outs	3 (6.7)	6 (12.2)	2 (3.4)	17 (17.3)
Remission (PASI 100)				
N (%) in analysis (NRI)	45 (100)	49 (100)	58 (100)	98 (100)
Replaced values (NRI), n (%)	2 (4.4)	6 (12.2)	4 (6.9)	19 (19.4)
Scalp IGA[a]				
N (%) in analysis (NRI)	43 (95.6)	40 (81.6)	54 (93.1)	89 (90.8)
Replaced values (NRI), n (%)	2 (4.4)	5 (10.2)	4 (6.9)	15 (15.3)
ppIGA[a]				
N (%) in analysis (NRI)	11 (24.4)	8 (16.3)	13 (22.4)	17 (17.3)
Replaced values (NRI), n (%)	0 (0)	0 (0)	2 (3.4)	4 (4.1)
mNAPSI 100[b]				
N (%) in analysis (NRI)	29 (64.4)	24 (49.0)	29 (50.0)	41 (41.8)
Replaced values (NRI), n (%)	2 (4.4)	2 (4.1)	2 (3.4)	8 (8.2)
PSD (all domains[c])				
N (%) in analysis (NRI)	44 (97.8)	48 (98.0)	58 (100)	98 (100)
Replaced values (NRI), n (%)	15 (33.3)	13 (26.5)	4 (6.9)	19 (19.4)
DLQI ≤ 1				
N (%) in analysis (NRI)	45 (100)	49 (100)	58 (100)	98 (100)
Replaced values (NRI), n (%)	2 (4.4)	6 (12.2)	4 (6.9)	19 (19.4)
Health status (EQ-5D VAS)				
N (%) in analysis at last time point	43 (95.6)	43 (87.8)	54 (93.1)	79 (80.6)
SF-36 PCS/MCS				
N (%) in analysis at last time point	43 (95.6)	43 (87.8)	Not recorded	Not recorded

a. Operationalized as scalp IGA or ppIGA = 0; only patients who had scalp involvement or ppIGA at baseline (scalp IGA ≥ 2 or ppIGA ≥ 2) were analysed.
b. Only patients with fingernail involvement at baseline (mNAPSI > 0) were analysed.
c. Operationalized as domain score = 0. The BE SURE study surveyed 14 domains, but the company presented data only on the domains of itching, pain, scaling, redness and burning. The BE RADIANT study surveyed only the 3 domains of itching, pain, and scaling.

DLQI: Dermatology Life Quality Index; IGA: Investigator's Global Assessment; MCS: Mental Component Summary; mNAPSI: modified Nail Psoriasis Severity Index; N: number of analysed patients; n: number of analysed patients with event; NRI: Non-Responder Imputation; PASI: Psoriasis Area and Severity Index; PCS: Physical Component Summary; ppIGA: palmoplantar IGA; PSD: psoriasis diary; SF-36: Short Form 36-Item Health Survey; VAS: visual analogue scale

Certainty of conclusions

As described in Section 2.3.1.1, the BE RADIANT study is used as the anchor for the qualitative summary. The assessment of extent and certainty of conclusions was initially based on the results of the BE RADIANT study, which is of higher informative value. The results of the study of higher informative value were not called into question by the BE SURE study. If the results of both studies are statistically significant and have the same direction of effects, the results of the BE SURE study can increase the certainty of conclusions of the BE RADIANT study, provided no other aspects reduce the certainty or results. However, the fact that the available results offer different qualitative certainties of results is to be taken into account.

Due to the high risk of bias of results regarding the morbidity and health-related quality of life outcomes, at most hints, e.g. of added benefit, can be derived for these outcomes from each of the 2 studies. In the present research question, however, higher-level uncertainties were found with regard to the subpopulation submitted by the company on research question 1 (see Section 2.3.1.2). Therefore, at most hints, e.g. of added benefit, can be derived, even if the results of both studies are statistically significant and exhibit the same direction of effect.

For the outcomes on all-cause mortality and side effects, at most indications, e.g. of added benefit, can be derived for each of the studies because of the low risk of bias of results. At most indications, e.g. of added benefit, can be derived even from the overall analysis of both studies because of the higher-level uncertainties regarding the subpopulation.

2.3.2.3 Results

Table 13 and Table 14 summarize the results of the comparison of bimekizumab versus adalimumab (BE SURE) and secukinumab (BE RADIANT) in patients with moderate to severe plaque psoriasis who are not candidates for conventional treatment in the framework of initial systemic therapy. Where necessary, calculations conducted by IQWiG 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 added benefit. In addition, the results regarding the absence of symptoms on fingernails (mNAPSI 100) for patients with baseline psoriasis at the fingernails (mNAPSI > 0) as well as the results regarding the absence of symptoms on palms and soles (ppIGA = 0) for patients with baseline palmoplantar psoriasis of at least grade 2 (ppIGA ≥ 2) are presented as supplementary information (see Appendix B of the full dossier assessment).

Tables on common AEs, SAEs, and discontinuation due to AEs are presented in Appendix E of the full dossier assessment and change-over-time curves in Appendix C of the full dossier assessment.

Table 13: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab (research question 1: initial systemic therapy) (multipage table)

Outcome category Outcome Study	Bimekizumab		Adalimumab or secukinumab		Bimekizumab vs. adalimumab or secukinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Mortality					
All-cause mortality					
BE SURE (Week 24)	43	0 (0)	49	0 (0)	–
BE RADIANT (Week 48)	58	0 (0)	98	0 (0)	–
Morbidity					
Remission (PASI 100)					
BE SURE (Week 24)	45	26 (57.8)	49	7 (14.3)	4.01 [1.91; 8.41]; < 0.001
BE RADIANT (Week 48)	58	43 (74.1)	98	44 (44.9)	1.58 [1.21; 2.06]; 0.001
PASI 90 (presented as supplementary information)					
BE SURE (Week 24)	45	39 (86.7)	49	20 (40.8)	2.22 [1.53; 3.23]; < 0.001
BE RADIANT (Week 48)	58	51 (87.9)	98	69 (70.4)	1.20 [1.03; 1.40]; 0.033
PASI 75 (presented as supplementary information)					
BE SURE (Week 24)	45	42 (93.3)	49	27 (55.1)	1.73 [1.31; 2.28]; < 0.001
BE RADIANT (Week 48)	58	52 (89.7)	98	77 (78.6)	1.11 [0.98; 1.26]; 0.153
Absence of symptoms on the scalp (scalp IGA)[b]					
BE SURE (Week 24)	43	34 (79.1)	40	18 (45.0)	1.70 [1.18; 2.44]; 0.002
BE RADIANT (Week 48)	54	45 (83.3)	89	62 (69.7)	1.16 [0.97; 1.39]; 0.125
Absence of symptoms on palms and soles (ppIGA[c])					
BE SURE (Week 24)				No usable data	
BE RADIANT (Week 48)				No usable data	
Absence of symptoms on fingernails (mNAPSI 100)[d]					
BE SURE (Week 24)				No usable data	
BE RADIANT (Week 48)				No usable data	
Patient-reported absence of symptoms (PSD)[e]					
PSD itching					
BE SURE (Week 24)	44	11 (25.0)	48	8 (16.7)	1.60 [0.69; 3.75]; 0.270
BE RADIANT (Week 48)	58	44 (75.9)	98	51 (52.0)	1.38 [1.10; 1.74]; 0.010
PSD pain					
BE SURE (Week 24)	44	15 (34.1)	48	14 (29.2)	1.31 [0.74; 2.33]; 0.358
BE RADIANT (Week 48)	58	51 (87.9)	98	66 (67.3)	1.27 [1.07; 1.49]; 0.010
PSD scaling					
BE SURE (Week 24)	44	14 (31.8)	48	8 (16.7)	1.97 [0.91; 4.25]; 0.080
BE RADIANT (Week 48)	58	45 (77.6)	98	46 (46.9)	1.54 [1.21; 1.96]; < 0.001

Table 13: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab (research question 1: initial systemic therapy) (multipage table)

Outcome category Outcome Study	Bimekizumab		Adalimumab or secukinumab		Bimekizumab vs. adalimumab or secukinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
PSD redness					
BE SURE (Week 24)	44	11 (25.0)	48	9 (18.8)	1.38 [0.64; 2.97]; 0.416
BE RADIANT (Week 48)				Not recorded	
PSD burning					
BE SURE (Week 24)	44	15 (34.1)	48	12 (25.0)	1.48 [0.81; 2.74]; 0.212
BE RADIANT (Week 48)				Not recorded	
PSD - other scales					
BE SURE (Week 24)[f]				No data	
BE RADIANT (Week 48)				Not recorded	
Patient-reported symptoms					
Patient Global Assessment					
BE SURE (Week 24)				No data	
BE RADIANT (Week 48)				No data	
Health-related quality of life					
DLQI ≤ 1					
BE SURE (Week 24)	45	29 (64.4)	49	18 (36.7)	1.78 [1.15; 2.76]; 0.007
BE RADIANT (Week 48)	58	49 (84.5)	98	70 (71.4)	1.13 [0.97; 1.33]; 0.153
Side effects					
AEs (supplementary information)[g]					
BE SURE (Week 24)	43	28 (65.1)	49	34 (69.4)	–
BE RADIANT (Week 48)	58	48 (82.8)	98	77 (78.6)	–
SAEs[g,h]					
BE SURE (Week 24)	43	0 (0)	49	0 (0)	–
BE RADIANT (Week 48)	58	4[i] (6.9)	98	0 (0)	NC; 0.003
Discontinuation due to AEs[h]					
BE SURE (Week 24)	43	1 (2.3)	49	2 (4.1)	0.58 [0.04; 7.75]; 0.682
BE RADIANT (Week 48)	58	0 (0)	98	3 (3.1)	NC; 0.234
Infections and infestations (SOC, AE)					
BE SURE (Week 24)	43	21 (48.8)	49	23 (46.9)	1.04 [0.68; 1.58]; 0.865
BE RADIANT (Week 48)	58	36 (62.1)	98	44 (44.9)	1.34 [1.00; 1.80]; 0.058
Fungal infectious disorders (HLGT, AE)[j]					
BE SURE (Week 24)	43	7 (16.3)	49	1 (2.0)	7.05 [0.97; 51.04]; 0.019
BE RADIANT (Week 48)	58	13 (22.4)	98	9 (9.2)	2.33 [1.04; 5.19]; 0.035

Table 13: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab (research question 1: initial systemic therapy) (multipage table)

Outcome category Outcome Study	Bimekizumab		Adalimumab or secukinumab		Bimekizumab vs. adalimumab or secukinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]

a. RR and CI: CMH test with region as stratification variable; p-value: CMH test for general association. Missing values for morbidity and health-related quality of life outcomes were replaced using non-responder imputation (NRI).
b. Operationalized as score = 0 with simultaneous improvement by at least 2 scale points at baseline. The instrument was surveyed over the course of the study only in patients exhibiting baseline scalp involvement. The analysis included only patients with grade ≥ 2 at baseline.
c. Operationalized as score = 0 with simultaneous improvement by at least 2 scale points at baseline. The instrument was surveyed over the course of the study only in patients exhibiting baseline palm and sole involvement. This applied to only 20% of randomized patients in BE SURE and 19% in BE RADIANT. The results are presented only as supplementary information in the appendix of the full dossier assessment.
d. The instrument was surveyed over the course of the study only in patients exhibiting baseline fingernail involvement. This applied to 56% of randomized patients in BE SURE and 45% in BE RADIANT. The results are presented only as supplementary information in the appendix of the full dossier assessment.
e. Operationalized as score = 0 for all symptoms.
f. In BE SURE, the following scales were additionally surveyed: cracking, dryness, irritation, sensitivity, lesions, thickening, fatigue, embarrassment, and choice of clothing.
g. Excluding disease-related events.
h. RR and 95% CI not meaningfully calculable.
i. Patients' documented SAEs were "dengue fever", "latent tuberculosis", "foot infected with necrotizing bacteria" and "car accident with C6 and T5 fracture".
j. HLGT "fungal infectious disorders"; results are largely based on the PT "oral candidiasis".

AE: adverse event; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; HLGT: high-level group term; IGA: Investigator's Global Assessment; mNAPSI: modified Nail Psoriasis Severity Index; n: number of patients with (at least 1) event; N: number of analysed patients; PASI: Psoriasis Area and Severity Index; ppIGA: palmoplantar IGA; PSD: psoriasis diary; PT: preferred term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab (research question 1: initial systemic therapy)

Outcome category Outcome Study	Bimekizumab			Adalimumab or secukinumab			Bimekizumab vs. adalimumab or secukinumab
	N[a]	Values at baseline mean (SD)	Change by treatment end[b] mean[c] (standard error, SE)	N[a]	Values at baseline mean (SD)	Change by treatment end[b] mean[c] (SE)	MD [95% CI][c]; p-value
Morbidity							
Health status (EQ-5D VAS)[d]							
BE SURE (Week 24)	43	76.6 (16.4)	9.8 (2.2)	43	75.9 (17.5)	3.8 (2.1)	6.02 [0.73; 11.31]; 0.026 Hedges' g 0.47 [0.05; 0.90][e]
BE RADIANT (Week 48)	54	80.3 (18.6)	8.2 (1.8)	79	78.0 (20.4)	7.2 (1.4)	0.93 [-3.54; 5.40]; 0.682
Health-related quality of life							
SF-36 PCS[f]							
BE SURE (Week 24)	43	49.7 (8.5)	5.6 (1.0)	43	47.0 (11.2)	5.3 (1.0)	0.35 [-1.82; 2.52]; 0.750
BE RADIANT (Week 48)	Outcome not recorded						
SF-36 MCS[g]							
BE SURE (Week 24)	43	52.8 (10.2)	2.3 (1.1)	43	53.7 (9.1)	2.5 (1.1)	-0.21 [-2.66; 2.25]; 0.868
BE RADIANT (Week 48)	Outcome not recorded						

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. For BE SURE, at 24 Weeks, and for BE RADIANT, at 48 Weeks.
c. Changes, mean differences, and CIs; MMRM with treatment, visit, treatment*visit, region, and value at treatment start as fixed effects, visit as repeat measurement and patient as random effect.
d. Higher (increasing) values indicate improved symptoms; positive effects (bimekizumab minus adalimumab or secukinumab) indicate an advantage for bimekizumab (scale range of 0 to 100).
e: Hedges' g, IQWiG calculation.
f. Higher (increasing) values indicate better health-related quality of life; positive effects (bimekizumab minus adalimumab or secukinumab) indicate an advantage for bimekizumab (scale range of 7–70).
g. Higher (increasing) values indicate better health-related quality of life; positive effects (bimekizumab minus adalimumab or secukinumab) indicate an advantage for bimekizumab (scale range of 6–70).

CI: confidence interval; MCS: Mental Component Summary; MD: mean difference; MMRM: mixed effect model repeated measurement; N: number of analysed patients; PCS: Physical Component Summary; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SF-36: Short Form 36 – version 2 Health Survey; VAS: visual analogue scale

On the basis of the available information, as described in Sections 2.3.1.2 and 2.3.2.2., the overall analysis of the BE RADIANT and BE SURE studies can derive at most hints, e.g. of added benefit, for morbidity and health-related quality of life outcomes. For the all-cause mortality and side effects outcomes, at most indications, e.g. of an added benefit, can be determined.

Mortality

All-cause mortality

No deaths had occurred in the BE SURE and BE RADIANT studies by Week 24 and Week 48, respectively. For all-cause mortality, this results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Remission (PASI 100)

A statistically significant effect was found in favour of bimekizumab for the outcome of remission, surveyed with the PASI 100. However, this effect is smaller in the determinative BE RADIANT study than it is in BE SURE. This results in a hint of added benefit of bimekizumab in comparison with the ACT for the outcome of remission.

Absence of symptoms on the scalp (scalp IGA = 0)

At Week 24, the BE SURE study shows a statistically significant difference in favour of bimekizumab versus adalimumab for the outcome of absence of symptoms on the scalp (scalp IGA = 0). However, there was no statistically significant difference between treatment arms in the determinative BE RADIANT study. Due to the lack of advantage in the determinative BE RADIANT study, this results in a hint of added benefit of bimekizumab in comparison with the ACT for this outcome; an added benefit is therefore not proven.

Absence of symptoms on palms and soles (pp IGA = 0) and absence of symptoms on fingernails (mNAPSI 100)

No usable data were available for the outcomes of absence of symptoms on palms and soles (ppIGA 0) and absence of symptoms on fingernails (mNAPSI 100). For its analyses, the company used the subpopulation of patients with baseline palmoplantar psoriasis grade 2 or higher or with baseline nail psoriasis (mNAPSI > 0). These analyses disregarded a substantial proportion of randomized patients and were therefore unsuitable for the derivation of the added benefit (see Section 2.3.2.2). For the outcomes absence of symptoms on palms and soles (ppIGA = 0) and absence of symptoms on fingernails (mNAPSI 100), this results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Patient-reported absence of symptoms

PSD itching, PSD pain

At Week 48, the BE RADIANT study showed a statistically significant difference in favour of bimekizumab versus secukinumab for the outcomes of PSD itching and PSD pain. This difference is no more than marginal, however. There was no statistically significant difference between BE SURE treatment arms for either outcome. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

PSD scaling

At Week 48, the determinative BE RADIANT study showed a statistically significant difference between treatment arms in favour of bimekizumab versus secukinumab for the outcome of PSD scaling. However, no statistically significant difference between treatment arms was found in the BE SURE study. This results in a hint of added benefit of bimekizumab in comparison with the ACT.

PSD redness

For the outcome of PSD redness, no statistically significant difference between treatment arms was found in the BE SURE study. The outcome was not recorded in the BE RADIANT study. This results in no hint of added benefit of bimekizumab in comparison with adalimumab; an added benefit is therefore not proven.

PSD burning

For the outcome of PSD burning, no statistically significant difference between treatment arms was found in the BE SURE study. The outcome was not recorded in the BE RADIANT study. This results in no hint of added benefit of bimekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Further patient-reported absence of symptoms (other PSD scales)

Regarding further outcomes on patient-reported absence of symptoms (particularly cracking and bleeding), the company's dossier does not provide any data for the BE SURE study, and the outcomes were not surveyed in the BE RADIANT study (see Section 2.3.2.1). This results in no hint of an added benefit of bimekizumab in comparison with adalimumab for further outcomes of patient-reported symptoms (particularly cracking and bleeding); an added benefit is therefore not proven.

Patient-reported symptoms (Patient Global Assessment)

The company presented no analyses on the outcome of Patient Global Assessment. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

For the outcome of health status, measured with EQ-5D VAS, the BE SURE study shows a statistically significant difference between treatment arms in favour of bimekizumab versus adalimumab. No statistically significant difference between treatment arms was found for the determinative BE RADIANT study. However, the 95% CI of the SMD (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. The observed can therefore not be inferred to be relevant. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

DLQI ≤ 1

For the outcome of health-related quality of life, measured with DLQI, the analysis shows a statistically significant difference between treatment arms in favour of bimekizumab versus adalimumab only for the BE SURE study. No statistically significant difference between treatment arms was found for the determinative BE RADIANT study. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

SF-36

For the outcome of health-related quality of life, measured with SF-36, the BE SURE study shows no statistically significant difference between treatment arms for either of the two summary scores (PCS or MCS). The outcome was not recorded in the BE RADIANT study. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, the determinative BE RADIANT study shows a statistically significant difference to the disadvantage of bimekizumab by Week 48. No SAEs occurred in the BE SURE study up to and including Week 24. This results in a hint of greater harm from bimekizumab in comparison with the ACT.

Discontinuation due to AEs and infections and infestations (SOC, AE)

Neither study showed any statistically significant difference between treatment arms for the outcomes of discontinuation due to AEs or infections and infestations (AE). This results in no hint of greater or lesser harm from bimekizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Fungal infectious disorders (HLGT, AE)

For the outcome of fungal infectious disorders (AE), both studies show a statistically significant difference between treatment arms to the disadvantage of bimekizumab versus adalimumab or secukinumab. However, the extent of the effect is no more than marginal in both studies. This

results in no hint of greater or lesser harm from bimekizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

2.3.2.4 Subgroups and other effect modifiers

The following effect modifiers were considered to be relevant for the present benefit assessment:

- age (< 40 years / 40 to < 65 years / ≥ 65 years)
- sex (female/male)
- disease severity (PASI < 20 / PASI ≥ 20)

All mentioned subgroup characteristics and thresholds had been prespecified for the total populations of both studies. The company submitted subgroup analyses for all outcomes listed in the dossier.

The descriptions of the subgroup analyses for binary and continuous outcomes as provided in Module 4 A are not plausible. IQWiG calculations show that for binary outcomes, the company used the Breslow-Day test for homogeneity of odds ratios (ORs). What would be required, however, is a test for subgroup effects regarding the effect measure of relative risk (RR). The 2 effect measures can lead to different results in the evaluation of an effect modification. For continuous outcomes, the company reportedly used the term subgroup*treatment*visit in the framework of a mixed effect model repeated measurement (MMRM). The concrete implementation of the p-value calculation for subgroup effects was not described. It also remains unclear how the interaction term is to be interpreted. For the reasons described, the subgroup analyses are unusable and have been disregarded for the benefit assessment.

2.3.3 Probability and extent of added benefit

The probability and extent of added benefit are derived below for research question 1 (adult patients who are not candidates for conventional treatment in the framework of initial systemic therapy) at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [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.

2.3.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.3.2 (see Table 15).

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

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

The baseline data were used for assessing the severity of the symptoms. The median PASI score at study start was below 20 in all study arms (BE SURE: 17.1 in the bimekizumab arm versus 16.3 in the adalimumab arm; BE RADIANT: 16.9 in the bimekizumab arm versus 17.4 in the secukinumab arm). Thus, for the majority of participants, PASI scores are within the non-serious range [14,17]. For these patients, the outcome of remission (PASI 100) was therefore allocated to the category of non-serious/non-severe symptoms / late complications.

This allocation deviates from the company's evaluation in that the company allocated the outcome of remission to the serious category.

Determination of outcome category for the outcomes on patient-reported absence of symptoms (PSD itching, PSD pain, and PSD scaling)

For determining the outcome category for PSD itching, PSD pain, and PSD scaling, the patients' baseline situation is relevant. For research question 1, the corresponding scores at baseline in both studies were between 6.0 and 6.8 for PSD itching and PSD scaling. For PSD pain, the baseline value in the BE SURE study was 5.6 in the bimekizumab arm and 4.6 in the adalimumab arm, and in the BE RADIANT study, 3.8 in the bimekizumab arm and 4.2 in the secukinumab arm. Based on these scores, the outcomes were assigned to the category of non-serious/non-severe symptoms / late complications.

To define the outcome category for the outcomes of PSD itching, PSD pain, and PSD scaling, the company used thresholds to distinguish serious from non-serious symptoms. The company defined these thresholds based on data from the BE SURE, BE VIVID and BE READY studies, with the aid of the Youden Index and 2 other methods for sensitivity analyses [21], and using DLQI question 1 as the anchor.

Irrespective of any methodological examination, this approach is unsuitable for determining a threshold because the anchor used does not adequately reflect the individual symptoms of itching, pain, and scaling. The outcomes of PSD itching, PSD pain, and PSD scaling are therefore assigned to the category of non-serious/non-severe symptoms / late complications.

For the outcomes of PSD itching and PSD scaling, this allocation departs from the company's, which placed these outcomes in the serious category.

Table 15: Extent of added benefit on outcome level: bimekizumab vs. adalimumab or secukinumab (research question 1: initial systemic therapy) (multipage table)

Outcome category **Outcome**	**Bimekizumab vs. adalimumab or secukinumab** **Proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality		
BE SURE	0% vs. 0% RR: –	Lesser/added benefit not proven
BE RADIANT		
Morbidity		
Remission (PASI 100)		
BE SURE	57.8% vs. 14.3% RR: 4.01 [1.91; 8.41] RR: 0.25 [0.12; 0.52][c] p < 0.001	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.90$ Added benefit; extent: minor
BE RADIANT	74.1% vs. 44.9% RR: 1.58 [1.21; 2.06] RR: 0.63 [0.49; 0.83][c] p = 0.001	
	probability: hint[d]	
Absence of symptoms on the scalp (scalp IGA)		
BE SURE	79.1% vs. 45.0% RR: 1.70 [1.18; 2.44] RR: 0.59 [0.41; 0.85][c] p = 0.002	Lesser/added benefit not proven
BE RADIANT	83.3% vs. 69.7% RR: 1.16 [0.97; 1.39] p = 0.125	
Absence of symptoms on the palms and soles (ppIGA)		
BE SURE	No usable data	Lesser/added benefit not proven
BE RADIANT		
Absence of symptoms on fingernails (mNAPSI 100)		
BE SURE	No usable data	Lesser/added benefit not proven
BE RADIANT		
PSD itching		
BE SURE	25.0% vs. 16.7% RR: 1.60 [0.69; 3.75] p = 0.270	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[e]
BE RADIANT	75.9% vs. 52.0% RR: 1.38 [1.10; 1.74] RR: 0.72 [0.75; 0.91][c] p = 0.010	

Table 15: Extent of added benefit on outcome level: bimekizumab vs. adalimumab or secukinumab (research question 1: initial systemic therapy) (multipage table)

Outcome category **Outcome**	**Bimekizumab vs. adalimumab or secukinumab** **Proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
PSD pain		
BE SURE	34.1% vs. 29.2% RR: 1.31 [0.74; 2.33] p = 0.358	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[e]
BE RADIANT	87.9% vs. 67.3% RR: 1.27 [1.07; 1.49] RR: 0.79 [0.67; 0.93][c] p = 0.010	
PSD scaling		
BE SURE	31.8% vs. 16.7% RR: 1.97 [0.91; 4.25] p = 0.080	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.90$ Added benefit; extent: minor
BE RADIANT	77.6% vs. 46.9% RR: 1.54 [1.21; 1.96] RR: 0.65 [0.51; 0.83][c] p < 0.001	
	Probability: hint	
PSD redness		
BE SURE	25.0% vs. 18.8% RR: 1.38 [0.64; 2.97] p = 0.416	Lesser/added benefit not proven
BE RADIANT	Not recorded	
PSD burning		
BE SURE	34.1% vs. 25.0% RR: 1.48 [0.81; 2.74] p = 0.212	Lesser/added benefit not proven
BE RADIANT	Not recorded	
PSD other scales		
BE SURE	No data	Lesser/added benefit not proven
BE RADIANT	Not recorded	
Patient-reported symptoms (Patient Global Assessment)		
BE SURE	No data	Lesser/added benefit not proven
BE RADIANT		

Table 15: Extent of added benefit on outcome level: bimekizumab vs. adalimumab or secukinumab (research question 1: initial systemic therapy) (multipage table)

Outcome category **Outcome**	**Bimekizumab vs. adalimumab or secukinumab** **Proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Health status (EQ-5D VAS)		
BE SURE	9.8 vs. 3.8 MD: 6.02 [0.73; 11.31]; p = 0.026 Hedges' g: 0.47 [0.05; 0.90][f]	Lesser/added benefit not proven
BE RADIANT	8.2 vs. 7.2 MD: 0.93 [-3.54; 5.40]; p = 0.682	
Health-related quality of life		
DLQI ≤ 1		
BE SURE	64.4% vs. 36.7% RR: 1.78 [1.15; 2.76] RR: 0.56 [0.36; 0.87][c] p = 0.007	Lesser/added benefit not proven
BE RADIANT	84.5% vs. 71.4% RR: 1.13 [0.97; 1.33] p = 0.153	
SF-36 PCS		
BE SURE	5.6 vs. 5.3 MD: 0.35 [-1.82; 2.52]; p = 0.750	Lesser/added benefit not proven
BE RADIANT	Outcome not recorded	
SF-36 MCS		
BE SURE	2.3 vs. 2.5 MD: -0.21 [-2.66; 2.25]; p = 0.868	Lesser/added benefit not proven
BE RADIANT	Outcome not recorded	
Side effects		
SAEs		
BE SURE	0% vs. 0% RR: –	Outcome category: serious/severe side effects greater harm; extent: non-quantifiable
BE RADIANT	6.9% vs. 0% RR: NC p = 0.003	
	Probability: hint	

Table 15: Extent of added benefit on outcome level: bimekizumab vs. adalimumab or secukinumab (research question 1: initial systemic therapy) (multipage table)

Outcome category **Outcome**	**Bimekizumab vs. adalimumab or secukinumab** **Proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Discontinuation due to AEs		
BE SURE	2.3% vs. 4.1% RR: 0.58 [0.04; 7.75] p = 0.682	Greater/lesser harm not proven
BE RADIANT	0% vs. 3.1% RR: NC p = 0.234	
Infections and infestations (AE)		
BE SURE	48.8% vs. 46.9% RR: 1.04 [0.68; 1.58] p = 0.865	Greater/lesser harm not proven
BE RADIANT	62.1% vs. 44.9% RR: 1.34 [1.00; 1.80] p = 0.058	
Fungal infectious disorders (AE)		
BE SURE	16.3% vs. 2.0% RR: 7.05 [0.97; 51.04] RR: 0.14 [0.02; 1.03][c] p = 0.019	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.00$ Greater/lesser harm not proven[e]
BE RADIANT	22.4% vs. 9.2% RR: 2.33 [1.04; 5.19] RR: 0.43 [0.19; 0.96][c] p = 0.035	

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. IQWiG calculation; reversed direction of effect to enable use of limits to derive the extent of added benefit.
d. Uncertainties in the formation of the subpopulation led to reduced certainty of conclusions (see Section 2.3.1.2).
e. The extent of the effect in this non-serious/non-severe outcome is no more than marginal.
f. If the CI for 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 inferred.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; DLQI: Dermatology Life Quality Index; MCS: Mental Component Summary; MD: mean difference; mNAPSI: modified Nail Psoriasis Area and Severity index; NC: not calculable; PASI: Psoriasis Area and Severity Index; PCS: Physical Component Summary; ppIGA: palmoplantar IGA; PSD: psoriasis diary; RR: relative risk; SAE: serious adverse event; SF-36: Short Form 36-Item Health Survey; VAS: visual analogue scale

2.3.3.2 Overall conclusion on added benefit

Table 16 summarizes the results included in the overall conclusion on the extent of added benefit.

Table 16: Favourable and unfavourable effects from the assessment of bimekizumab in comparison with adalimumab or secukinumab (research question 1: initial systemic therapy)

Favourable effects	Unfavourable effects
Non-serious/non-severe symptoms / late complications ▪ Remission (PASI 100): hint of an added benefit – extent: minor ▪ PSD scaling: hint of an added benefit – extent: minor	
	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: non-quantifiable
Despite having surveyed them, the company submitted no data on the outcome of patient-reported symptoms (Patient Global Assessment) nor data on patient-reported absence of symptoms (PSD scales, BE SURE study).	
PASI: Psoriasis Area and Severity Index; PSD: psoriasis diary; SAE: serious adverse event	

Overall, this results in both favourable effects in the outcome category of non-serious/non-severe symptoms / late complications and an unfavourable effect in the outcome category of serious/severe side effects.

For each of the outcomes of remission PASI 100 and PSD scaling, there is a hint of minor added benefit of bimekizumab in comparison with adalimumab or secukinumab. For the outcome of SAEs, there is a hint of greater harm, but its extent is non-quantifiable. This greater harm does not fully call into question the advantage in the outcomes of remission PASI 100 and PSD scaling.

In summary, for adult patients who are not candidates for conventional therapy in the framework of initial systemic therapy (research question 1), there is a hint of minor added benefit of bimekizumab in comparison with the ACT.

The above assessment deviates from the company's, which derived proof of considerable added benefit of bimekizumab for the present benefit assessment.

2.4 Research question 2: adult patients with inadequate response or intolerance to prior 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 bimekizumab (status: 2 July 2021)
- bibliographical literature search on bimekizumab (last search on 5 July 2021)
- search in trial registries / trial results databases for studies on bimekizumab (last search on 5 July 2021)
- search on the G-BA website for bimekizumab (last search on 2 July 2021)

To check the completeness of the study pool:

- search in trial registries for studies on bimekizumab (last search on 7 September 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

2.4.1.1 Studies included

As was the case for research question 1 (adult patients who are not candidates for conventional treatment in the framework of initial systemic therapy), the benefit assessment of bimekizumab in adult patients with moderate to severe plaque psoriasis with inadequate response or intolerance to prior systemic therapy (research question 2) included the studies BE SURE and BE RADIANT. (See Table 5 regarding the study pool.)

In addition to the BE SURE and BE RADIANT studies, for research question 2, the appendix of Module 4 B of the company's dossier additionally presents BE VIVID study results, but the company did not use them for deriving an added benefit of bimekizumab. The BE VIVID study compares bimekizumab with ustekinumab, another ACT option listed by the G-BA for research question 2. Since in this study, bimekizumab was consistently administered at 4-week intervals, which is in violation of the SPC, this study was disregarded for the benefit assessment. However, the effects it showed are in the same direction as those in the BE SURE and BE RADIANT studies.

2.4.1.2 Study characteristics

The characteristics of the BE SURE and BE RADIANT studies are described in Table 6 and Table 7 under research question 1. The design of the studies is described in Section 2.3.1.2 under research question 1.

Subpopulation relevant for research question 2

Research question 2 of this benefit assessment comprises patients with moderate to severe plaque psoriasis with inadequate response or intolerance to prior systemic therapy. Consequently, only subpopulations of the BE SURE and the BE RADIANT studies were relevant for the present research question. The company has formed these subpopulations by including patients who had received prior systemic psoriasis therapy and had discontinued it due to inadequate response and/or intolerance. Patients whose discontinuation of prior systemic therapy was due to other reasons were excluded. A comparison with the respective study report

shows that both studies originally included substantially more pretreated patients and that prior treatment was likely discontinued for reasons other than intolerance or inadequate response. The company did not present any corresponding information in Module 4 B. This makes it impossible to determine why the patients in the subpopulation discontinued their prior treatment and whether their exclusion from research question 2 is justified.

The subpopulation used for research question 2 comprises 87 patients in the bimekizumab arm and 84 patients in the adalimumab arm of the BE SURE study, which corresponds to approximately half of the patients originally randomized to these study arms. In the BE RADIANT study, the same was true for about 60% of patients, at 128 patients in the bimekizumab arm and 228 patients in the secukinumab arm.

Table 17 shows the patient characteristics for the relevant subpopulation of the included studies.

Table 17: Characteristics of the study populations – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab (research question 2: inadequate response or intolerance to prior treatment) (multipage table)

Study	BE SURE		BE RADIANT	
Characteristic	Bimekizumab	Adalimumab	Bimekizumab	Secukinumab
Category	N[a] = 87	N[a] = 84	N[a] = 128	N[a] = 228
Age [years], mean (SD)	43 (13)	46 (14)	45 (14)	44 (14)
Sex [f/m], %	36/64	31/69	30/70	36/64
Body weight [kg], mean (SD)	92.2 (27.1)	88.1 (20.0)	88.3 (20.3)	88.2 (19.5)
Weight [kg], n (%)				
≤ 100	62 (71)	61 (73)	91 (71)	180 (79)
> 100	25 (29)	23 (27)	37 (29)	48 (21)
Ancestry, n (%)				
White	80 (92)	75 (89)	123 (96)	218 (96)
Asian	2 (2)	7 (8)	1 (1)	4 (2)
Other	5 (6)[b]	2 (2)[b]	4 (3)[b]	6 (3)[b]
Region, n (%)				
North America	24 (28)	25 (30)	26 (20)	60 (26)
Western Europe	11 (13)	15 (18)	40 (31)	56 (25)
Central and Eastern Europe	46 (53)	39 (46)	56 (44)	98 (43)
Asia and Australia	6 (7)	5 (6)	6 (5)	14 (6)
PASI, mean (SD)	21.0 (6.7)	18.9 (5.6)	20.7 (7.8)	20.1 (7.0)
PASI, median [min; max]	19.8 [12.0; 42.6]	17.4 [12.0; 34.8]	18.8 [12.0; 62.4]	18.2 [11.8; 53.1]
PASI, n (%)				
< 20	46 (53)	58 (69)	77 (60)	140 (61)
≥ 20	41 (47)	26 (31)	51 (40)	88 (39)
Fingernail involvement (mNAPSI > 0), n (%)				
Yes	47 (54)	58 (69)	75 (59)	114 (50)
No	40 (46)	26 (31)	53 (41)	114 (50)
Fingernail involvement (mNAPSI), mean (SD)[c]	25.3 (22.5)	20.5 (19.7)	19.4 (19.9)	19.7 (19.1)
Scalp involvement (scalp IGA grade), n (%)[d]				
0 (clear)	2 (2)	7 (8)	6 (5)	16 (7)
1 (almost clear)	1 (1)	1 (1)	10 (8)	8 (4)
2 (mild)	20 (23)	16 (19)	22 (17)	37 (16)
3 (moderate)	53 (61)	47 (56)	72 (56)	135 (59)
4 (severe)	11 (13)	12 (14)	18 (14)	31 (14)

Table 17: Characteristics of the study populations – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab (research question 2: inadequate response or intolerance to prior treatment) (multipage table)

Study	BE SURE		BE RADIANT	
Characteristic	Bimekizumab	Adalimumab	Bimekizumab	Secukinumab
Category	N[a] = 87	N[a] = 84	N[a] = 128	N[a] = 228
Palm and sole involvement (ppIGA grade), n (%)[d]				
0 (clear)	52 (60)	56 (67)	92 (72)	152 (67)
1 (almost clear)	9 (10)	5 (6)	6 (5)	11 (5)
2 (mild)	7 (8)	12 (14)	15 (12)	27 (12)
3 (moderate)	11 (13)	5 (6)	11 (9)	33 (14)
4 (severe)	8 (9)	5 (6)	4 (3)	4 (2)
Psoriatic arthritis (PGADA > 0)				
Yes	71 (82)	66 (79)	88 (69)	164 (72)
No	16 (18)	18 (21)	40 (31)	64 (28)
DLQI, mean (SD)	11.2 (6.0)	11.3 (7.7)	11.1 (7.2)	11.9 (7.6)
Diagnosis of disease [years ago], mean (SD)	19.0 (10.9)	17.9 (11.9)	20.9 (12.4)	19.0 (12.5)
Severity (IGA grade), n (%)[e]				
3 (moderate)	55 (63)	61 (73)	82 (64)	167 (73)
4 (severe)	32 (37)	23 (27)	46 (36)	61 (27)
Prior lines of therapy, n (%)				
Conventional systemic therapy[f]	ND	ND	ND	ND
Phototherapy or photochemotherapy[g]	ND	ND	ND	ND
Biologic therapy	27 (31)	34 (40)	49 (38)	87 (38)
Apremilast	3 (3)	4 (5)	9 (7)	14 (6)
Treatment discontinuation, n (%)	ND	ND	ND	ND
Study discontinuation, n (%)[h]	5 (6)	3 (4)	8 (6)[i]	22 (10)[i]

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. Including Black / Native Hawaiian or Other Pacific Islander / Other / Mixed; IQWiG calculation
c. Only patients who had fingernail involvement at baseline.
d. IQWiG calculation of percentages based on the number of randomized patients; in both control arms, values are missing for 1 patient each.
e. According to both studies' inclusion criteria, only patients with IGA ≥ 3 were to be included.
f. Data available only for failed conventional systemic therapy; in the BE SURE study, this was the case for 83 patients (95%) in the intervention arm and 82 patients (98%) in the control arm. In the BE RADIANT study, it applied to 123 patients (96%) in the intervention arm and 217 (95%) in the control arm. It is unclear whether intolerance was included under failed therapy.
g. Failed phototherapy or photochemotherapy had been received, in the BE SURE study, by 51 patients (58.6%) in the intervention arm and 61 patients (72.6%) in the control arm. In the BE RADIANT study, this applied to 79 patients (61.7%) in the intervention arm and 140 (61.4%) in the control arm.
h. No deaths occurred in either study.
i. At Week 48.

Table 17: Characteristics of the study populations – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab (research question 2: inadequate response or intolerance to prior treatment) (multipage table)

Study Characteristic Category	BE SURE		BE RADIANT	
	Bimekizumab	Adalimumab	Bimekizumab	Secukinumab
	N[a] = 87	N[a] = 84	N[a] = 128	N[a] = 228
f: female; IGA: Investigator's Global Assessment; m: male; max: maximum; min: minimum; mNAPSI: modified Nail Psoriasis Severity Index; n: number of patients in the category; N: number of randomized patients; ND: no data; PASI: Psoriasis Area and Severity Index; PGADA: Patient Global Assessment of Disease Activity; ppIGA: palmoplantar IGA; RCT: randomized controlled trial; SD: standard deviation				

The patient characteristics of the subpopulations are largely comparable, both between studies and between treatment arms. This applies to both demographic and disease characteristics. The patients in the relevant subpopulation had a mean age of 44 years, about two-thirds of them were female, and over 90% were of white ancestry.

Patients' mean PASI was between 17 and 20, and slightly more than half exhibited fingernail involvement. More than 70% of patients had moderate to severe scalp involvement, and they had been diagnosed with the disease about 19 years prior to enrolment. The percentage of patients with concomitant psoriatic arthritis was slightly higher in the BE SURE study, at about 80%, than in the BE RADIANT study, at about 70%. Almost all patients had already received conventional systemic therapy, and between 31% and 40% had already received biologic therapy.

Risk of bias across outcomes (study level)

As already described in Section 2.3.2.2 on research question 1, the risk of bias at study level for BE SURE and BE RADIANT was rated as low for both studies. This concurs with the company's assessment (see Table 9).

Transferability of the study results to the German health care context

The information provided by the company regarding the transferability of study results to the German health care context is described in Section 2.3.2.2 on research question 1.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The patient-relevant outcomes listed in Section 2.3.2.1 for research question 1 were to be taken into account in the assessment of research question 2. Like for research question 1, the assessment of research question 2 did not involve a metaanalytic summary of the BE SURE and BE RADIANT studies (for the reasoning and approach used in the qualitative summary of results, see Section 2.3.2.1).

The choice of patient-relevant outcomes departs from the choice made by the company, which used further outcomes in the dossier (Module 4 B) (see Section 2.3.2.1 on research question 1). Table 10 on research question 1 shows the outcomes for which data were available in the included studies. As described in Section 2.3.2.1 on research question 1, the company's dossier does not provide usable data for all outcomes listed in Table 10. This is additionally discussed below for research question 2.

Morbidity – patient-reported symptoms (Patient Global Assessment)

For patient-reported symptoms (Patient Global Assessment), which according to the study protocols was surveyed in both studies, the company's Module 4 B did not include any analyses for the relevant subpopulations.

Morbidity – absence of symptoms on the scalp, fingernails, palms, soles (scalp IGA, mNAPSI 100 and ppIGA)

For the dossier, the company has presented a post hoc analysis which defines response as the achievement of scalp IGA grade 0 with simultaneous improvement by at least 2 points. According to the study protocols, response was originally defined as achieving grade 0 (clear) or 1 (almost clear). However, only a clear scalp (IGA = 0) was deemed patient-relevant since for the other scale values, the burden placed on patients by the remaining symptoms remains unclear. The present operationalization is therefore unsuitable for the benefit assessment.

For the outcome of absence of symptoms on the scalp (scalp IGA = 0), only part of the population was included in the analysis, namely only patients with at least IGA grade 2 at baseline. While an analysis on the basis of all randomized patients would have been necessary, the outcome was included in the assessment because a sufficient percentage of patients of at least 80% was included in the analysis (see Table 18).

Both studies' results on absence of symptoms on fingernails (mNAPSI 100) and palms and soles (ppIGA = 0) were unusable because they were surveyed only in patients already been affected at study start. For instance, baseline ppIGA had to be at least 2 and baseline mNAPSI at least 1 for the respective patient to be included in the analysis (see Section 2.3.2.2). For both outcomes, fewer than 70% of study participants were therefore included in the analysis (see Table 19). The analyses presented by the company for mNAPSI 100 and ppIGA were therefore disregarded for the present benefit assessment. See the supplementary information provided in Appendix B of the full dossier assessment for the results on mNAPSI 100 and ppIGA.

2.4.2.2 Risk of bias

Table 18 describes the risk of bias for the results of the relevant outcomes.

Table 18: Risk of bias at study and outcome levels – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab (research question 2: inadequate response or intolerance to prior treatment)

Study		Outcomes													
	Study level	All-cause mortality	Remission (PASI 100[a])	Patient-reported absence of symptoms (PSD[b])	Patient-reported symptoms (Patient Global Assessment)	Absence of symptoms on the scalp (scalp IGA[c])	Absence of symptoms on palms and soles (ppIGA[c])	Absence of symptoms on fingernails (mNAPSI 100[a])	Health-related quality of life (DLQI[d])	Health-related quality of life (SF-36)	Health status (EQ-5D VAS)	SAEs	Discontinuation due to AEs	Infections and infestations (SOC, AEs)	Fungal infectious disorders (HLGT, AE)[e]
BE SURE	L	L	L	H[f]	–[g]	L	–[h]	–[h]	L	L	L	L	L	L	L
BE RADIANT	L	L	L	L	–[g]	H[i]	–[h]	–[h]	L	–[j]	H[i]	L	L	L	L

a. Score improvement by 100% from baseline.
b. Operationalized as domain score = 0. The BE SURE study surveyed 14 domains, of which the company presented data only on the domains of itching, pain, scaling, redness and burning; the BE RADIANT study surveyed only the 3 domains of itching, pain, and scaling.
c. Operationalized as scalp IGA or ppIGA = 0.
d. Operationalized as DLQI ≤ 1.
e. HLGT "fungal infectious disorders".
f. High percentages of NRI-replaced values; see Table 19.
g. No usable data available; for reasoning, see Section 2.4.2.2 of the present dossier assessment.
h. No usable data available; for a discussion, see Section 2.4.2.2 of the present dossier assessment.
i. > 10% missing values in analysis; see Table 19.
j. Outcome not surveyed.

AE: adverse event; DLQI: Dermatology Life Quality Index; H: high; HLGT: high level group term; IGA: Investigator's Global Assessment; L: low; mNAPSI: modified Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index; pp: palmoplantar; PSD: psoriasis diary; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form 36-Item Health Survey; SOC: system organ class; VAS: visual analogue scale

For research question 2, the risk of bias for the results of the outcome of patient-reported absence of symptoms, surveyed using the PSD, is rated as high in the BE SURE study. This is due to the high percentage of NRI-replaced values (almost 30%; see Table 19). NRI rates patients with missing values as non-responders. As in research question 1 (see Section 2.3.2.2), missing values may be due to reasons other than nonresponse. According to Module 4 B of the company's dossier, the BE SURE study's patient population for research question 2 exhibited, up to Week 24, only 1 study discontinuation due to lack of response per treatment arm. In the BE RADIANT study, 4 patients were documented as discontinuing the study early due to lack of response up to and including Week 48, all of whom were in the secukinumab arm. The

BE RADIANT results on the outcomes of absence of symptoms on the scalp (scalp IGA = 0) and health condition (EQ-5D VAS) are also rated as potentially highly biased because > 10% of patients were disregarded in the analysis (see Table 19).

The sensitivity analyses presented by the company's Module 4 A (observed case analyses [BE SURE, BE RADIANT], multiple imputation [BE RADIANT]) are unsuitable for increasing the certainty of conclusions for the outcomes on symptoms and health-related quality of life because they take into account only patients with certain baseline scores or because the percentage of missing values is too high and differs between arms.

The risk of bias for the results of all other outcomes is rated as low in both studies.

Table 19: Overview of replaced values in individual outcomes of the BE SURE and BE RADIANT studies for evaluating the risk of bias on the outcome level (research question 2: inadequate response or intolerance to prior therapy)

Outcome Time point (replacement strategy)	BE SURE		BE RADIANT	
	Bimekizumab (N = 87)	Adalimumab (N = 84)	Bimekizumab (N = 128)	Secukinumab (N = 228)
Study discontinuations	5 (5.7)	3 (3.6)	8 (6.3)	22 (9.6)
Remission (PASI 100)				
N (%) in analysis (NRI)	87 (100)	84 (100)	128 (100)	228 (100)
Replaced values (NRI), n (%)	6 (6.9)	5 (6.0)	12 (9.4)	27 (11.8)
Scalp IGA[a]				
N (%) in analysis (NRI)	84 (96.6)	75 (89.3)	112 (87.5)	203 (89.0)
Replaced values (NRI), n (%)	6 (6.9)	5 (6.0)	12 (9.4)	23 (10.1)
ppIGA[a]				
N (%) in analysis (NRI)	26 (29.9)	22 (26.2)	30 (23.4)	64 (28.1)
Replaced values (NRI), n (%)	2 (2.3)	3 (3.6)	2 (1.6)	9 (3.9)
mNAPSI 100[b]				
N (%) in analysis (NRI)	47 (54.0)	58 (69.0)	75 (58.6)	114 (50.0)
Replaced values (NRI), n (%)	4 (4.6)	4 (4.8)	7 (5.5)	11 (4.8)
PSD (all domains[c])				
N (%) in analysis (NRI)	86 (98.9)	81 (96.4)	128 (100)	228 (100)
Replaced values (NRI), n (%)	26 (29.9)	24 (28.6)	12 (9.4)	28 (12.3)
DLQI ≤ 1				
N (%) in analysis (NRI)	87 (100)	84 (100)	128 (100)	228 (100)
Replaced values (NRI), n (%)	8 (9.2)	7 (8.3)	12 (9.4)	28 (12.3)
Health status (EQ-5D VAS)				
N (%) in analysis at last time point	79 (90.8)	76 (90.5)	116 (90.6)	200 (87.7)
SF-36 PCS / MCS				
N (%) in analysis at last time point	79 (90.8)	76 (90.5)	Not recorded	Not recorded

a. Operationalized as scalp IGA or ppIGA = 0; only patients who had scalp involvement or ppIGA at baseline (scalp IGA ≥ 2 or ppIGA ≥ 2) were analysed.
b. Only patients with fingernail involvement at baseline (mNAPSI > 0) were analysed.
c. Operationalized as domain score = 0. The BE SURE study surveyed 14 domains, but the company presented data only on the domains of itching, pain, scaling, redness and burning. The BE RADIANT study surveyed only the 3 domains of itching, pain, and scaling.

DLQI: Dermatology Life Quality Index; IGA: Investigator's Global Assessment; MCS: Mental Component Summary; mNAPSI: modified Nail Psoriasis Severity Index; N: number of analysed patients; n: number of analysed patients with event; NRI: Non-Responder Imputation; PASI: Psoriasis Area and Severity Index; PCS: Physical Component Summary; ppIGA: palmoplantar IGA; PSD: psoriasis diary; SF-36: Short Form 36-Item Health Survey; VAS: visual analogue scale

Certainty of conclusions

As described in Section 2.3.1.1, the BE RADIANT study is used as the anchor for the qualitative summary. The assessment of extent as well as certainty of conclusions was initially based on the results of the BE RADIANT study, which has a higher informative value. The results of the study of higher informative value were not called into question by the BE SURE study. If the results of both studies are statistically significant and have the same direction of effects, the results of the BE SURE study can increase the certainty of conclusions of the BE RADIANT study, provided no other aspects reduce the certainty or results.

Due to the low risk of bias of results, on the basis of the available information from the BE RADIANT study, indications, e.g. of added benefit, can be derived for the outcomes of all-cause mortality, remission (PASI 100), patient-reported absence of symptoms (PSD), health-related quality of life (DLQI ≤ 1), SAEs, discontinuation due to AEs, and all specific AEs. Given the absence of any other aspects reducing the certainty of conclusions for the present research question 2, the results of the BE SURE study can increase the certainty of conclusions of the BE RADIANT study in the overall analysis of both studies, so that proof can be derived for these outcomes (for reasoning, see Section 2.3.2.1).

Due to the high risk of bias of results in the outcomes of absence of symptoms on the scalp (scalp IGA = 0) and health status (EQ-5D VAS), at most hints, e.g. of added benefit, can be derived for the BE RADIANT study; for the BE SURE study, in contrast, indications can be derived due to the low risk of bias. If the results of both studies point in the same direction and are statistically significant, the certainty of the BE SURE study's results can be upgraded here as well, so that the overall analysis of both studies can derive indications for these outcomes. The outcome of health-related quality of life (SF-36) was surveyed only in the BE SURE study. The risk of bias for this outcome was low; therefore, an indication, e.g. of added benefit, can be derived for this outcome.

2.4.2.3 Results

Table 20 and Table 21 summarize the results of the comparison of bimekizumab versus adalimumab (BE SURE) or secukinumab (BE RADIANT) in patients with moderate to severe plaque psoriasis with inadequately response or intolerance to prior systemic therapy. Where necessary, calculations conducted by IQWiG 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 used for the derivation of added benefit. In addition, the results on absence of symptoms on fingernails (mNAPSI 100) as well as absence of symptoms on palms and soles (ppIGA = 0) are presented as supplementary information in Appendix B of the full dossier assessment.

Tables on common AEs, SAEs, and discontinuation due to AEs are presented in Appendix E of the full dossier assessment and change-over-time curves in Appendix D of the full dossier assessment.

For common SAEs, the company's Module 4 B uses a threshold of occurrence in at least 5% of patients, disregarding the fact that events which occurred in at least 10 patients should be listed as well. This remains without consequence since the 5%-threshold translates into more than 10 patients only for the BE RADIANT comparator arm, where it would result in 11 patients, constituting a small difference.

Table 20: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab (research question 2: inadequate response or intolerance to prior treatment) (multipage table)

Outcome category Outcome Study	Bimekizumab		Adalimumab or secukinumab		Bimekizumab vs. adalimumab or secukinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Mortality					
All-cause mortality					
BE SURE (Week 24)	83	0 (0)	84	0 (0)	–
BE RADIANT (Week 48)	128	1 (0.8)	228	1 (0.4)	1.54 [0.13; 18.63]; 0.733
Morbidity					
Remission (PASI 100)					
BE SURE	87	59 (67.8)	84	33 (39.3)	1.69 [1.24; 2.30]; < 0.001
BE RADIANT (Week 48)	128	79 (61.7)	228	109 (47.8)	1.29 [1.07; 1.56]; 0.010
PASI 90 (presented as supplementary information)					
BE SURE (Week 24)	87	77 (88.5)	84	50 (59.5)	1.46 [1.20; 1.78]; < 0.001
BE RADIANT (Week 48)	128	108 (84.4)	228	160 (70.2)	1.19 [1.06; 1.33]; 0.004
PASI 75 (presented as supplementary information)					
BE SURE (Week 24)	87	81 (93.1)	84	64 (76.2)	1.22 [1.06; 1.40]; 0.003
BE RADIANT (Week 48)	128	115 (89.8)	128	187 (82.0)	1.09 [1.00; 1.18]; 0.062
Clear scalp (scalp-IGA)[b]					
BE SURE (Week 24)	84	71 (84.5)	75	50 (66.7)	1.28 [1.05; 1.55]; 0.008
BE RADIANT (Week 48)	112	87 (77.7)	203	150 (73.9)	1.05 [0.92; 1.19]; 0.493
Absence of symptoms on palms and soles (ppIGA[c])					
BE SURE (Week 24)				No usable data	
BE RADIANT (Week 48)				No usable data	
Absence of symptoms on fingernails (mNAPSI 100)[d]					
BE SURE (Week 24)				No usable data	
BE RADIANT (Week 48)				No usable data	
Patient-reported absence of symptoms (PSD)[e]					
PSD itching					
BE SURE (Week 24)	86	30 (34.9)	81	18 (22.2)	1.57 [0.95; 2.60]; 0.076
BE RADIANT (Week 48)	128	77 (60.2)	228	106 (46.5)	1.28 [1.05; 1.57]; 0.018
PSD pain					
BE SURE (Week 24)	86	44 (51.2)	81	28 (34.6)	1.44 [1.00; 2.08]; 0.041
BE RADIANT (Week 48)	128	104 (81.3)	228	164 (71.9)	1.12 [1.00; 1.25]; 0.070
PSD scaling					
BE SURE (Week 24)	86	37 (43.0)	81	19 (23.5)	1.86 [1.15; 2.99]; 0.007
BE RADIANT (Week 48)	128	90 (70.3)	228	117 (51.3)	1.36 [1.15; 1.61]; < 0.001

Table 20: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab (research question 2: inadequate response or intolerance to prior treatment) (multipage table)

Outcome category Outcome Study	Bimekizumab		Adalimumab or secukinumab		Bimekizumab vs. adalimumab or secukinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
PSD redness					
BE SURE (Week 24)	86	36 (41.9)	81	17 (21.0)	2.06 [1.25; 3.40]; 0.003
BE RADIANT (Week 48)				Not recorded	
PSD burning					
BE SURE (Week 24)	86	39 (45.3)	81	28 (34.6)	1.29 [0.88; 1.89]; 0.178
BE RADIANT (Week 48)				Not recorded	
PSD - other scales					
BE SURE (Week 24)[f]				No data	
BE RADIANT (Week 48)				Not recorded	
Patient-reported symptoms					
Patient Global Assessment					
BE SURE (Week 24)				No data	
BE RADIANT (Week 48)				No data	
Health-related quality of life					
DLQI ≤ 1					
BE SURE (Week 24)	87	59 (67.8)	84	44 (52.4)	1.29 [1.01; 1.65]; 0.042
BE RADIANT (Week 48)	128	101 (78.9)	228	157 (68.9)	1.13 [1.00; 1.29]; 0.060
Side effects					
AEs (presented as supplementary information)[g]					
BE SURE (Week 24)	83	58 (69.9)	84	59 (70.2)	–
BE RADIANT (Week 48)	128	110 (85.9)	228	191 (83.8)	–
SAEs[g]					
BE SURE (Week 24)	83	1 (1.2)	84	4 (4.8)	0.26 [0.03; 2.64]; 0.206
BE RADIANT (Week 48)	128	8 (6.3)	228	19 (8.3)	0.74 [0.33; 1.65]; 0.455
Discontinuation due to AEs					
BE SURE (Week 24)	83	1 (1.2)	84	2 (2.4)	0.41 [0.04; 4.54]; 0.459
BE RADIANT (Week 48)	128	2 (1.6)	228	6 (2.6)	0.59 [0.12; 2.78]; 0.498
Infections and infestations (SOC, AE)					
BE SURE (Week 24)	83	47 (56.6)	84	42 (50.0)	1.13 [0.85; 1.49]; 0.401
BE RADIANT (Week 48)	128	89 (69.5)	228	135 (59.2)	1.15 [0.99; 1.35]; 0.076
Fungal infectious disorders (HLGT, AE)[h]					
BE SURE (Week 24)	83	13 (15.7)	84	0 (0)	27.32 [1.65; 452.23][i]; < 0.001
BE RADIANT (Week 48)	128	50 (39.1)	228	22 (9.6)	3.83 [2.47; 5.96]; < 0.001

Table 20: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab (research question 2: inadequate response or intolerance to prior treatment) (multipage table)

Outcome category Outcome Study	Bimekizumab		Adalimumab or secukinumab		Bimekizumab vs. adalimumab or secukinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]

a. RR and CI: CMH test with region as stratification variable; p-value: CMH test for general association. Missing values for morbidity and health-related quality of life outcomes were replaced using non-responder imputation (NRI).
b. Operationalized as score = 0 with simultaneous improvement by at least 2 scale points at baseline. The instrument was surveyed over the course of the study only in patients with baseline scalp involvement. The analysis included only patients with baseline grade ≥ 2.
c. Operationalized as score = 0 with simultaneous improvement by at least 2 scale points at baseline. The instrument was surveyed over the course of the study only in patients with baseline palm and sole involvement. This applied to 28% of randomized patients in BE SURE and 26% in BE RADIANT. The results are presented only as supplementary information in the appendix of the full dossier assessment.
d. The instrument was surveyed over the course of the study only in patients exhibiting baseline fingernail involvement. This applied to 61% of randomized patients in BE SURE and 53% in BE RADIANT. The results are presented only as supplementary information in the appendix of the full dossier assessment.
e. Operationalized as score = 0 for all symptoms.
f. In BE SURE, the following scales were additionally surveyed: cracking, dryness, irritation, sensitivity, lesions, thickening, fatigue, embarrassment, and choice of clothing.
g. Excluding disease-related events.
h. HLGT "fungal infectious disorders"; the results are largely based on the PT of "oral candiasis".
i. IQWiG calculation; RR and 95% CI asymptotic with continuity correction of 0.5; p-value unconditional exact test (CSZ method according to [22]).

AE: adverse event; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; HLGT: high-level group term; IGA: Investigator's Global Assessment; mNAPSI: modified Nail Psoriasis Severity Index; n: number of patients with (at least 1) event; N: number of analysed patients; PASI: Psoriasis Area and Severity Index; ppIGA: palmoplantar IGA; PSD: psoriasis diary; PT: preferred term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 21: Results (mortality, morbidity, health-related quality of life, continuous) – RCT, direct comparison: bimekizumab vs. adalimumab or secukinumab (research question 2: inadequate response or intolerance to prior treatment)

Outcome category Outcome Study	Bimekizumab			Adalimumab or secukinumab			Bimekizumab vs. adalimumab or secukinumab
	N[a]	Values at baseline mean (SD)	Change by treatment end[b] mean[c] (SE)	N[a]	Values at baseline mean (SD)	Change by treatment end[b] mean[c] (SE)	MD [95% CI][c]; p-value
Morbidity							
Health status (EQ-5D VAS)[d]							
BE SURE	79	76.6 (16.7)	12.0 (1.6)	76	71.5 (18.6)	8.4 (1.5)	3.55 [-0.64; 7.74]; 0.096
BE RADIANT	116	71.5 (20.9)	12.6 (1.4)	200	73.0 (20.9)	11.0 (1.0)	1.59 [-1.71; 4.88]; 0.344
Health-related quality of life							
SF-36 PCS[e]							
BE SURE	79	50.7 (8.5)	5.5 (0.6)	76	48.2 (10.0)	4.4 (0.6)	1.02 [-0.71; 2.75]; 0.246
BE RADIANT	Outcome not recorded						
SF-36 MCS[f]							
BE SURE	79	52.1 (8.8)	4.1 (0.7)	76	52.8 (8.4)	2.2 (0.6)	1.93 [0.20; 3.67]; 0.029 Hedges' g[g]: 0.35 [0.03; 0.67]
BE RADIANT	Outcome not recorded						

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. For BE SURE, at 24 Weeks, and for BE RADIANT, at 48 Weeks.
c. Changes, mean differences, and CIs; MMRM with treatment, visit, treatment*visit, region, and value at treatment start as fixed effects, visit as repeat measurement and patient as random effect.
d. Higher (increasing) values indicate improved symptoms; positive effects (bimekizumab minus adalimumab or secukinumab) indicate an advantage for bimekizumab (scale range of 0 to 100).
e. Higher (increasing) values indicate better health-related quality of life; positive effects (bimekizumab minus adalimumab or secukinumab) indicate an advantage for bimekizumab (scale range of 7–70).
f. Higher (increasing) values indicate better health-related quality of life; positive effects (bimekizumab minus adalimumab or secukinumab) indicate an advantage for bimekizumab (scale range of 6–70).
g: Hedges' g, IQWiG calculation.

CI: confidence interval; MCS: Mental Component Summary; MD: mean difference; MMRM: mixed effect model repeated measurement; N: number of analysed patients; PCS: Physical Component Summary; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SF-36: Short Form 36 – version 2 Health Survey; VAS: visual analogue scale

As described in Section 2.3.1.2 and given that no further aspects reduce the certainty of conclusions in the present research question 2, the available information in the overall analysis of the BE RADIANT and BE SURE studies can be used to derive at most proof, e.g. of added benefit, for the outcomes of all-cause mortality, remission (PASI 100), patient-reported absence

of symptoms (PSD), health-related quality of life (DLQI ≤ 1), SAEs, discontinuation due to AEs, and all specific AEs. For the all-cause mortality and side effects outcomes, at most indications, e.g. of an added benefit, can be determined. For the outcomes of absence of symptoms on the scalp (scalp IGA = 0) and health status (EQ-5D VAS), at most indications, e.g. of added benefit, can be derived. The outcome of health-related quality of life (SF-36) was surveyed only in the BE SURE study. The risk of bias for this outcome was low; therefore, an indication, e.g. of added benefit, can be derived for this outcome.

Mortality

All-cause mortality

For the outcome of all-cause mortality, no statistically significant difference between treatment arms was found in the BE RADIANT study. No deaths occurred in the BE SURE study. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Remission (PASI 100)

For the outcome of remission, surveyed with the PASI 100, both studies showed a statistically significant difference between treatment arms. However, this difference is at most minor in the determinative BE RADIANT study. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Absence of symptoms on the scalp (scalp IGA = 0)

At Week 24, the BE SURE study shows a statistically significant difference in favour of bimekizumab versus adalimumab for the outcome of absence of symptoms on the scalp (scalp IGA = 0). However, no statistically significant difference between treatment arms was found for the determinative BE RADIANT study. Due to the lack of an advantage in the determinative BE RADIANT study, this results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Absence of symptoms on palms and soles (ppIGA = 0) and absence of symptoms on fingernails (mNAPSI 100)

No usable data were available for the outcomes of absence of symptoms on palms and soles (ppIGA 0) and absence of symptoms on fingernails (mNAPSI 100). For its analyses, the company used the subpopulation of patients with baseline palmoplantar psoriasis grade 2 or higher or with baseline nail psoriasis (mNAPSI > 0). These analyses disregarded a substantial proportion of randomized patients and were therefore unsuitable for the derivation of the added benefit (see Section 2.4.2.2). This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Patient-reported absence of symptoms

PSD itching

For the outcome of PSD itching, the BE RADIANT study shows a statistically significant difference between treatment arms. This difference is no more than marginal, however. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

PSD pain

For the outcome of PSD pain, the BE RADIANT study shows no statistically significant difference between treatment arms. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

PSD scaling

For the outcome of PSD scaling, a statistically significant difference between treatment arms was found for both studies in favour of bimekizumab versus adalimumab or secukinumab. This results in proof of added benefit of bimekizumab in comparison with the ACT.

PSD redness

For the outcome of PSD redness, the BE SURE study shows a statistically significant difference between treatment arms in favour of bimekizumab versus adalimumab. The outcome was not recorded in the BE RADIANT study. This results in a hint of an added benefit of bimekizumab in comparison with adalimumab.

PSD burning

For the outcome of PSD burning, the BE SURE study shows no statistically significant difference between treatment arms. The outcome was not recorded in the BE RADIANT study. This results in no hint of added benefit of bimekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Further patient-reported absence of symptoms (other PSD scales)

According to protocol, the BE SURE study surveyed further scales of patient-reported absence of symptoms. However, the company's dossier presents no data on this outcome for the relevant subpopulation (see Section 2.4.2.2). The BE RADIANT study did not survey any other scales of patient-reported absence of symptoms. This results in no hint of added benefit of bimekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Patient-reported symptoms (Patient Global Assessment)

According to protocol, both studies surveyed the outcome of patient-reported symptoms (Patient Global Assessment). However, the company's dossier presents no data on this outcome for the relevant subpopulation (see Section 2.4.2.2). This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

For the outcome of health status (EQ-5D VAS), no statistically significant difference between treatment arms was found for either study. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

DLQI ≤ 1

At Week 24, the BE SURE study showed a statistically significant difference in favour of bimekizumab versus adalimumab for the outcome of health-related quality of life, measured with DLQI. However, no statistically significant difference between treatment arms was found for the determinative BE RADIANT study. Due to the lack of an advantage in the determinative BE RADIANT study, this results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

SF-36 PCS

For the outcome of health-related quality of life, surveyed with SF-36, the BE SURE study's PCS shows no statistically significant difference between treatment arms. The outcome was not recorded in the BE RADIANT study. This results in no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

SF-36 MCS

For the outcome of health-related quality of life, surveyed with SF-36, the BE SURE study's MCS shows a statistically significant difference between treatment arms. The CI for Hedges' g, however, is not completely outside the irrelevance range [-0.2; 0.2]. It can therefore not be inferred that the effect was relevant. The outcome was not recorded in the BE RADIANT study. This results in no hint of added benefit of bimekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs, and infections and infestations (AE)

Neither study showed any statistically significant difference between treatment arms for the outcomes of SAEs, discontinuation due to AEs, or infections and infestations (AEs). This results in no hint of greater or lesser harm from bimekizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Fungal infectious disorders (AE)

For the outcome of fungal infectious disorders (AE), both studies show a statistically significant difference between treatment arms to the disadvantage of bimekizumab versus adalimumab or secukinumab. This results in proof of greater harm from bimekizumab in comparison with the ACT.

2.4.2.4 Subgroups and other effect modifiers

The following effect modifiers were considered to be relevant for the present benefit assessment:

- age (< 40 years / 40 to < 65 years / ≥ 65 years)
- sex (female/male)
- disease severity (PASI < 20 / PASI ≥ 20)

All mentioned subgroup characteristics and thresholds had been prespecified for the total populations of both studies. The company submitted subgroup analyses for all outcomes listed in the dossier.

The descriptions of binary and continuous outcomes included in the subgroup analyses of Module 4 B are implausible. IQWiG calculations show that for binary outcomes, the company used the Breslow-Day test for homogeneity of ORs. What would be required, however, is a test for subgroup effects regarding the effect measure of RR. The 2 effect measures can lead to different results in the evaluation of an effect modification. For continuous outcomes, the company reportedly used the term subgroup*treatment*visit within the context of a mixed effect model repeated measurement (MMRM). The concrete implementation of the p-value calculation for subgroup effects was not described. It also remains unclear how the interaction term is to be interpreted. For the reasons described, the subgroup analyses are unusable and have been disregarded for the benefit assessment.

2.4.3 Probability and extent of added benefit

The probability and extent of added benefit are derived below at the outcome level for research question 2 (adult patients with inadequately response or intolerance to prior systemic therapy), taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [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 2.4.2.3 (see Table 22).

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

As described in Section 2.3.3.1, the allocation of the outcome of remission (PASI 100) to an outcome category depends on the patients' initial situation, particularly on the severity and the grade of impairment from the symptoms measured with PASI (psoriatic plaque redness, thickness, and scaling).

The baseline data were used for assessing the severity of the symptoms. The median PASI value at study start is below 20 in all study arms (19.8 in the bimekizumab arm and 17.4 in the adalimumab arm of BE SURE; 18.8 in the bimekizumab arm and 18.2 in the secukinumab arm of BE RADIANT). Thus, for the majority of participants, PASI scores are within the non-serious range [14,17]. For these patients, the outcome of remission (PASI 100) was therefore allocated to the category of non-serious/non-severe symptoms / late complications.

This allocation deviates from the company's evaluation in that the company allocated the outcome of remission to the serious category.

Determination of the outcome category for the outcomes on patient-reported absence of symptoms (outcomes PSD itching, PSD scaling, and PSD redness)

For determining the outcome category for PSD itching, PSD scaling, and PSD redness, as described in Section 2.3.3.1, the patients' baseline situation is relevant. Regarding research question 2, the respective BE SURE baseline values for all 3 outcomes were about 7, and the BE RADIANT PSD itching and PSD scaling values were between 6.2 and 6.7. PSD redness was not surveyed in the latter study. Based on these values, the outcomes were assigned to the category of non-serious/non-severe symptoms / late complications.

To define the outcome categories for PSD itching, PSD scaling, and PSD redness, the company used thresholds to distinguish serious from non-serious symptoms. The company defined these thresholds based on data from the BE SURE, BE VIVID and BE READY studies, with the aid of the Youden Index and 2 other methods for sensitivity analyses [21], and using DLQI question 1 as the anchor.

Irrespective of a methodological examination, this approach is unsuitable for determining a threshold because the anchor used does not adequately reflect the individual symptoms of itching, scaling, and redness. The outcomes of PSD itching, PSD scaling ,and PSD redness are therefore allocated to the category of non-serious/non-severe symptoms / late complications.

This allocation deviates from the evaluation by the company, which allocated the outcomes to the serious category.

Table 22: Extent of added benefit at outcome level: bimekizumab vs. adalimumab or secukinumab (research question 2: inadequate response / intolerance to prior treatment) (multipage table)

Outcome category **Outcome**	**Bimekizumab vs. adalimumab or secukinumab** **Proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality		
BE SURE	0% vs. 0% RR: –	Lesser/added benefit not proven
BE RADIANT	0.8% vs. 0.4% RR: 1.54 [0.13; 18.63] p = 0.733	
Morbidity		
Remission (PASI 100)		
BE SURE	67.8% vs. 39.3% RR: 1.69 [1.24; 2.30] RR: 0.59 [0.43; 0.81][c] p < 0.001	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[d]
BE RADIANT	61.7% vs. 47.8% RR: 1.29 [1.07; 1.56] RR: 0.78 [0.64; 0.93][c] p = 0.010	
Absence of symptoms on the scalp (scalp IGA)		
BE SURE	84.5% vs. 66.7% RR: 1.28 [1.05; 1.55] RR: 0.78 [0.65; 0.95][c] p = 0.008	Lesser/added benefit not proven
BE RADIANT	77.7% vs. 73.9% RR: 1.05 [0.92; 1.19] p = 0.493	
Absence of symptoms on the palms and soles (ppIGA)		
BE SURE	No usable data	Lesser/added benefit not proven
BE RADIANT		
Absence of symptoms on fingernails (mNAPSI 100)		
BE SURE	No usable data	Lesser/added benefit not proven
BE RADIANT		

Table 22: Extent of added benefit at outcome level: bimekizumab vs. adalimumab or secukinumab (research question 2: inadequate response / intolerance to prior treatment) (multipage table)

Outcome category **Outcome**	**Bimekizumab vs. adalimumab or secukinumab** **Proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
PSD itching		
BE SURE	34.9% vs. 22.2% RR: 1.57 [0.95; 2.60] p = 0.076	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[d]
BE RADIANT	60.2% vs. 46.5% RR: 1.28 [1.05; 1.57] RR: 0.78 [0.64; 0.95][c] p = 0.018	
PSD pain		
BE SURE	51.2% vs. 34.6% RR: 1.44 [1.00; 2.08] RR: 0.69 [0.48; 1.00][c] p = 0.041	Lesser/added benefit not proven
BE RADIANT	81.3% vs. 71.9% RR: 1.12 [1.00; 1.25] p = 0.070	
PSD scaling		
BE SURE	43.0% vs. 23.5% RR: 1.86 [1.15; 2.99] RR: 0.54 [0.33; 0.87][c] p = 0.007	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Added benefit; extent: minor
BE RADIANT	70.3% vs. 51.3% RR: 1.36 [1.15; 1.61] RR: 0.74 [0.62; 0.87][c] p < 0.001	
	Probability: proof	
PSD redness		
BE SURE	41.9% vs. 21.0% RR: 2.06 [1.25; 3.40] RR: 0.49 [0.29; 0.80][c] p = 0.003	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Added benefit; extent: minor
BE RADIANT	Not recorded	
	Probability: hint[e]	

Table 22: Extent of added benefit at outcome level: bimekizumab vs. adalimumab or secukinumab (research question 2: inadequate response / intolerance to prior treatment) (multipage table)

Outcome category **Outcome**	**Bimekizumab vs. adalimumab or secukinumab** **Proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
PSD burning		
BE SURE	45.3% vs. 34.6% RR: 1.29 [0.88; 1.89] p = 0.178	Lesser/added benefit not proven
BE RADIANT	Not recorded	
PSD other scales		
BE SURE	No data	Lesser/added benefit not proven
BE RADIANT	Not recorded	
Patient-reported symptoms (Patient Global Assessment)		
BE SURE	No data	Lesser/added benefit not proven
BE RADIANT		
Health status (EQ-5D VAS)		
BE SURE	12.0 vs. 8.4 MD: 3.55 [-0.64; 7.74]; p = 0.096	Lesser/added benefit not proven
BE RADIANT	12.6 vs. 11.0 MD: 1.59 [-1.71; 4.88]; p = 0.344	
Health-related quality of life		
Response DLQI ≤ 1		
BE SURE	67.8% vs. 52.4% RR: 1.29 [1.01; 1.65] RR: 0.78 [0.61; 0.99][c] p = 0.042	Lesser/added benefit not proven
BE RADIANT	78.9% vs. 68.9% RR: 1.13 [1.00; 1.29] p = 0.060	
SF-36 PCS		
BE SURE	5.5 vs. 4.4 MD: 1.02 [-0.71; 2.75]; p = 0.246	Lesser/added benefit not proven
BE RADIANT	Outcome not recorded	

Table 22: Extent of added benefit at outcome level: bimekizumab vs. adalimumab or secukinumab (research question 2: inadequate response / intolerance to prior treatment) (multipage table)

Outcome category **Outcome**	**Bimekizumab vs. adalimumab or secukinumab** **Proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
SF-36 MCS		
BE SURE	4.1 vs. 2.2 MD: 1.93 [0.20; 3.67]; p = 0.029 Hedges' g: 0.35 [0.03; 0.67][f]	Lesser/added benefit not proven
BE RADIANT	Outcome not recorded	
Side effects		
SAEs		
BE SURE	1.2% vs. 4.8% RR: 0.26 [0.03; 2.64] p = 0.206	Greater/lesser harm not proven
BE RADIANT	6.3% vs. 8.3% RR: 0.74 [0.33; 1.65] p = 0.455	
Discontinuation due to AEs		
BE SURE	1.2% vs. 2.4% RR: 0.41 [0.04; 4.54] p = 0.459	Greater/lesser harm not proven
BE RADIANT	1.6% vs. 2.6% RR: 0.59 [0.12; 2.78] p = 0.498	
Infections and infestations (AE)		
BE SURE	56.6% vs. 50.0% RR: 1.13 [0.85; 1.49] p = 0.401	Greater/lesser harm not proven
BE RADIANT	69.5% vs. 59.2% RR: 1.15 [0.99; 1.35] p = 0.076	

Table 22: Extent of added benefit at outcome level: bimekizumab vs. adalimumab or secukinumab (research question 2: inadequate response / intolerance to prior treatment) (multipage table)

Outcome category **Outcome**	**Bimekizumab vs. adalimumab or secukinumab** **Proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Fungal infectious disorders (AE)		
BE SURE	15.7% vs. 0% RR: 27.32 [1.65; 452.23] RR: 0.04 [0.002; 0.61][c] p < 0.001	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: considerable
BE RADIANT	39.1% vs. 9.6% RR: 3.83 [2.47; 5.96] RR: 0.26 [0.17; 0.40][c] p < 0.001	
	Probability: proof	

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. IQWiG calculation; reversed direction of effect to enable use of limits to derive the extent of added benefit.
d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
e. Results for this outcome are available only from the BE SURE study. Due to the high risk of bias, at most a hint can be derived for this outcome (see Section 2.4.2.2).
f. If the CI for 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 inferred.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; DLQI: Dermatology Life Quality Index; MCS: Mental Component Summary; MD: mean difference; mNAPSI: modified Nail Psoriasis Area and Severity Index; PASI: Psoriasis Area and Severity Index; PCS: Physical Component Summary; ppIGA: palmoplantar IGA; PSD: psoriasis diary; RR: relative risk; SF-36: Short Form 36-Item Health Survey; SAE: severe adverse event; VAS: visual analogue scale

2.4.3.2 Overall conclusion on added benefit

Table 23 summarizes the results included in the overall conclusion on the extent of added benefit.

Table 23: Favourable and unfavourable effects from the assessment of bimekizumab in comparison with adalimumab or secukinumab (research question 2: inadequate response or intolerance to prior treatment)

Favourable effects	Unfavourable effects
Non-serious/non-severe symptoms / late complications ▪ PSD scaling: proof of added benefit – extent: minor ▪ PSD redness: hint of added benefit – extent: minor	Non-serious/non-severe side effects ▪ Fungal infectious disorders: proof of greater harm – extent: considerable
Despite having surveyed them, the company did not submit any data on the outcome of patient-reported symptoms (Patient Global Assessment) or data on patient-reported absence of symptoms (PSD scales, BE SURE study) (see Section 2.3.2.1).	
PASI: Psoriasis Area and Severity Index; PSD: psoriasis diary	

Overall, this results in both favourable effects regarding the outcome category of non-serious/non-severe symptoms / late complications as well as an unfavourable effect regarding the outcome category of non-serious/non-severe side effects.

For the outcomes of PSD scaling and PSD redness, proof and a hint of minor added benefit were found for bimekizumab in comparison with adalimumab or secukinumab, respectively. By contrast, proof of greater harm of considerable extent was found for the outcome of fungal infectious disorders.

In summary, taking into account the high percentage of fungal infectious disorders and the selective presentation of the PSD scales in patient-reported absence of symptoms (Table 22), for patients with moderate to severe plaque psoriasis with inadequate response or intolerance to prior systemic therapy (research question 2), there is no hint of added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

The above assessment deviates from the company's, which derived proof of considerable added benefit of bimekizumab for the present benefit assessment.

2.5 Probability and extent of added benefit – summary

Table 24 summarizes the result of the assessment of added benefit of bimekizumab in comparison with the ACT.

Table 24: Bimekizumab – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
1	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**	Hint of minor added benefit
2	Adult patients with moderate to severe plaque psoriasis with inadequate response or intolerance to prior systemic therapy	**Adalimumab** or brodalumab or guselkumab or infliximab or ixekizumab or risankizumab or **secukinumab** or ustekinumab	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to 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 the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. UCB Biopharma. A phase 3, multicenter, randomized, double-blind study with an active-controlled initial treatment period followed by a dose-blind maintenance treatment period to evaluate the efficacy and safety of Bimekizumab in adult subjects with moderate to severe chronic plaque psoriasis; study PS0008; Clinical Study Report [unpublished]. 2020.

4. UCB Biopharma. A Phase 3, Multicenter, Randomized, Double-Blind Study with an Active-Controlled Initial Treatment Period Followed by a Dose-Blind Maintenance Treatment Period to Evaluate the Efficacy and Safety of Bimekizumab in Adult Subjects with Moderate to Severe Chronic Plaque Psoriasis [online]. [Accessed: 10.09.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-003392-22.

5. UCB Biopharma. A Study to Evaluate the Efficacy and Safety of Bimekizumab in Adult Subjects With Moderate to Severe Chronic Plaque Psoriasis (BE SURE) [online]. 2021 [Accessed: 10.09.2021]. URL: https://ClinicalTrials.gov/show/NCT03412747.

6. Warren RB, Blauvelt A, Bagel J et al. Bimekizumab versus Adalimumab in Plaque Psoriasis. N Engl J Med 2021.

7. UCB Biopharma. A multicenter, randomized, double-blind, Secukinumab-controlled, parallel-group study to evaluate the efficacy and safety of Bimekizumab in adult subjects with moderate to severe chronic plaque psoriasis; study PS0015; Interim Clinical Study Report [unpublished]. 2020.

8. UCB Biopharma. A Multicenter, Randomized, Double-Blind, Secukinumab-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Bimekizumab in Adult Subjects With Moderate to Severe Chronic Plaque Psoriasis [online]. [Accessed: 10.09.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-003784-35.

9. UCB Biopharma. A Study to Evaluate the Efficacy and Safety of Bimekizumab Compared to an Active Comparator in Adult Subjects With Moderate to Severe Chronic Plaque Psoriasis (BE RADIANT) [online]. 2021 [Accessed: 10.09.2021]. URL: https://ClinicalTrials.gov/show/NCT03536884.

10. Reich K, Warren RB, Lebwohl M et al. Bimekizumab versus Secukinumab in Plaque Psoriasis. N Engl J Med 2021.

11. AbbVie Deutschland. Fachinformation Humira 40 mg/0,4 ml Injektionslösung in einer Fertigspritze, Humira 40 mg/0,4 ml Injektionslösung im Fertigpen (Stand 04/2021). 2021.

12. Novartis Europharm. Fachinformation Cosentyx 150 mg/-300 mg Injektionslösung in einer Fertigspritze, Cosentyx 150 mg/-300 mg Injektionslösung in einem Fertigpen (Stand 02/2021). 2021.

13. U. C. B. Pharma. Fachinformation Bimzelx (Stand 08/2021). 2021.

14. Committee for Medicinal Products for Human Use. Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis. 2004.

15. Mrowietz U, Kragballe K, Reich K et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res 2011; 303(1): 1-10.

16. Nast A, Smith C, Spuls PI et al. EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris - Part 1: treatment and monitoring recommendations. J Eur Acad Dermatol Venereol 2020; 34(11): 2461-2498. https://dx.doi.org/10.1111/jdv.16915.

17. Nast A, Altenburg L, Augustin M et al. Deutsche S3-Leitlinie zur Therapie der Psoriasis vulgaris, adaptiert von EuroGuiDerm. J Dtsch Dermatol Ges 2021.

18. Maul JT, Navarini AA, Sommer R et al. Gender and age significantly determine patient needs and treatment goals in psoriasis - a lesson for practice. J Eur Acad Dermatol Venereol 2019; 33(4): 700-708.

19. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Guselkumab (Plaque-Psoriasis) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2018 [Accessed: 23.11.2021]. URL: https://www.iqwig.de/download/a17-60_guselkumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

20. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Brodalumab (Plaque-Psoriasis) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2017 [Accessed: 23.11.2021]. URL: https://www.iqwig.de/download/a17-42_brodalumab_nutzenbewertung-35a-sgb-v_v1-1.pdf.

21. UCB. Statistical Report - Determination of thresholds defining severity levels for PSD item scores (studies: PS0008, PS0009, PS0015; product: Bimekizumab). 2021.

22. 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. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

The full report (German version) is published under https://www.iqwig.de/en/projects/a21-110.html.