

Bimekizumab (psoriatic arthritis)

Addendum to Project A23-60
(dossier assessment)¹



ADDENDUM

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

Phone: +49 221 35685-0

Fax: +49 221 35685-1

E-mail: berichte@iqwig.de

Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Alina Reese
- Lisa Junge
- Mattea Patt
- Daniela Preukschat

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD	biologic disease-modifying antirheumatic drug
BSA	body surface area
csDMARD	conventional synthetic disease-modifying antirheumatic drug
DAPSA	Disease Activity in Psoriatic Arthritis
DLQI	Dermatology Life Quality Index
DMARD	disease-modifying antirheumatic drug
FACIT	Functional Assessment of Chronic Illness Therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HAQ-DI	Health Assessment Questionnaire-Disability Index
HLGT	High Level Group Term
hsCRP	high-sensitivity C-reactive protein
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDI	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index
MedDRA	Medical Dictionary for Regulatory Activities
MDA	minimal disease activity
mNAPSI	modified Nail Psoriasis Severity Index
NRI	non-responder imputation
NRS	numeric rating scale
PASI	Psoriasis Area and Severity Index
PGA	Patient Global Assessment
PsA	psoriatic arthritis
PsAID-12	12-item Psoriatic Arthritis Impact of Disease
PsAQOL	Psoriatic Arthritis Quality of Life
PT	Preferred Term
PtAAP	Patient Assessment of Arthritis Pain
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short Form (36) Health Survey

Abbreviation	Meaning
SGB	Sozialgesetzbuch (Social Code Book)
SJC66	swollen joint count 66
SOC	System Organ Class
SPARCC	Spondyloarthritis Research Consortium of Canada
SPC	Summary of Product Characteristics
TJC68	tender joint count 68
VAS	visual analogue scale

1 Background

On 7 November 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-60 (Bimekizumab – Benefit assessment according to §35a Social Code Book V) [1].

In its comments, the pharmaceutical company (hereinafter referred to as “the company”) submitted supplementary information, which went beyond the information provided in the dossier, to prove the added benefit. The commission comprises the assessment of the data from the BE OPTIMAL study presented in the dossier [2], taking into account the information from the commenting procedure [3] and the data submitted after the oral hearing [4].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

For the benefit assessment of bimekizumab, the company used the randomized controlled trial (RCT) BE OPTIMAL for research question 1 (biologic disease-modifying antirheumatic drugs [bDMARD]-naive adults with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior DMARD therapy). Based on the information in the dossier, it was not sufficiently ensured that the subpopulation with ≥ 1 prior conventional synthetic disease-modifying antirheumatic drug (csDMARD) therapies presented by the company was suitable for the comparison of bimekizumab with adalimumab [1]. Firstly, this was due to the fact that it was not clear whether all patients in the subpopulation had had an inadequate response or had been intolerant to prior csDMARD therapy. Secondly, some of the patients in both study arms received csDMARD treatment that was not in compliance with the approval. Even though it was ensured for the latter point of criticism that at least 80% of the subpopulation were treated in accordance with the approval, it was overall unclear from the information in the dossier whether at least 80% of the patients in the subpopulation corresponded to the present research question. The subpopulation presented by the company was therefore not used for the benefit assessment.

In the commenting procedure [3] and after the oral hearing, the company submitted additional data [4] to show that the subpopulation it presented is suitable for answering research question 1. Furthermore, the company presented additional analyses on the outcomes of Leeds Dactylitis Index (LDI), serious adverse events (SAEs) and discontinuation due to adverse events (AEs).

There are still no data for research question 2 of the dossier assessment (patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior bDMARD therapy), so that there are no new aspects compared with the dossier assessment.

The following Sections 2.1 to 2.7 refer exclusively to research question 1 of dossier assessment A23-60 [1]. Section 2.8 contains a conclusion on the added benefit for both research questions.

2.1 Suitability of the subpopulation with ≥ 1 prior csDMARD therapies presented by the company

Based on the data subsequently submitted by the company in the commenting procedure and after the oral hearing, it is assessed below whether at least 80% of the subpopulation from the BE OPTIMAL study presented by the company fulfil the criteria of inadequate response or intolerance to a csDMARD and of use of the study medication in compliance with the approval, and whether the subpopulation is therefore suitable for the benefit assessment. The subpopulation presented by the company comprises 339 patients in the bimekizumab arm and 108 patients in the adalimumab arm.

Inadequate response to prior therapy with a csDMARD

In the commenting procedure, the company submitted data, which it used to infer that the patients of the presented subpopulation of the BE OPTIMAL study corresponded to research question 1 of the benefit assessment and had an inadequate response or had been intolerant to at least one prior csDMARD therapy.

For patients who were included in the BE OPTIMAL study in Europe, Canada, Japan or Australia, the inclusion criterion “eligibility for adalimumab therapy according to local approval” ensures that there was an inadequate response to prior therapy with a csDMARD (see A23-60 [1]). The subsequently submitted data show that this applies to 77.2% of the subpopulation (261 patients in the bimekizumab arm and 84 patients in the adalimumab arm).

The company clarified in the comments that in Russia, as in the United States [5], an inadequate response or intolerance to previous csDMARD therapy is not a prerequisite for treatment with adalimumab. Based on the guideline recommendations, however, 12 weeks is the minimum treatment duration after which therapy can be escalated if response is inadequate [6,7]. According to the inclusion criteria, patients had to have active psoriatic arthritis, defined as a swollen joint count (SJC) of at least 3 and a tender joint count (TJC) of at least 3, to be eligible for study participation; hence, patients with at least 12 weeks of treatment with a csDMARD can be assumed to have had an inadequate response to prior csDMARD therapy. Since the inclusion criteria permitted parallel administration of methotrexate or leflunomide only if it had been started at least 12 weeks before baseline and had been given with a stable dose for at least 8 weeks before randomization, a minimum treatment duration of 12 weeks is ensured for all patients with methotrexate sodium or leflunomide at baseline. In the bimekizumab arm, these were 58 out of a total of 78 patients included in the United States and Russia in the subpopulation presented, and in the adalimumab arm 20 out of 24 (a total of 17.4% of the subpopulation presented).

The subsequently submitted information on the duration of csDMARD pretreatment in the United States and Russia also implies a minimum treatment duration of 12 weeks for patients with sulfasalazine therapy at baseline. In the presented subpopulation, this applies to 6 patients in the bimekizumab arm and 2 in the adalimumab arm (1.8% in total).

The subsequently submitted data thus show that at least 431 patients (96.4%) of the subpopulation presented had an inadequate response or intolerance to at least one prior csDMARD therapy.

Use of csDMARDs was partly not in compliance with the approval

As described in dossier assessment A23-60 [1], some patients received concomitant treatment with a csDMARD that was not in compliance with the approval during the course of the BE OPTIMAL study. Firstly, the use of bimekizumab was not limited to monotherapy or a

combination with methotrexate, which is in compliance with the Summary of Product Characteristics (SPC). Secondly, the drugs sulfasalazine and hydroxychloroquine sulphate (bimekizumab arm only), which are not approved in the present therapeutic indication, were used. It was not clear from the information in the dossier how many patients in the bimekizumab arm received another csDMARD in addition to methotrexate or switched to a concomitant treatment that was not in compliance with the approval during the course of the study.

The company addressed this uncertainty and, following the oral hearing, submitted information on concomitant therapy with methotrexate or methotrexate sodium, sulfasalazine and leflunomide (including combinations of these drugs) or on monotherapy at baseline and at Week 16, 24, 36 and 52. Table 1 shows the number of patients in the bimekizumab arm who were receiving no csDMARD or only methotrexate or only methotrexate sodium as concomitant treatment, in compliance with the approval of bimekizumab [8], at the respective time points. The company did not provide any explicit information for the subpopulation on how many patients switched their concomitant treatment during the entire duration of the study. However, the subsequently submitted data show that the proportion of patients in the bimekizumab arm treated in compliance with the approval increased from 82.9% at baseline to 87.6% at Week 52. The number of patients with concomitant therapy with methotrexate or methotrexate sodium decreased by Week 52, while at the same time the number of patients without concomitant therapy increased to a similar extent. Based on the subsequently submitted data, it appears sufficiently certain that 281 patients (82.9%) in the bimekizumab arm were treated in compliance with the approval, despite the lack of information on treatment switches over the entire course of the study.

Table 1: Information on the approval-compliant concomitant csDMARD therapy in the bimekizumab arm of the RCT BE OPTIMAL

Study	Patients with therapy n (%)
Bimekizumab N = 339	
BE OPTIMAL	
At baseline	
No csDMARD ^b	38 (11.2)
Methotrexate only	218 (64.3)
Methotrexate sodium only	25 (7.4)
At Week 16	
No csDMARD ^b	56 (16.5)
Methotrexate only	209 (61.7)
Methotrexate sodium only	24 (7.1)
At Week 24	
No csDMARD ^b	70 (20.6)
Methotrexate only	196 (57.8)
Methotrexate sodium only	24 (7.1)
At Week 36	
No csDMARD ^b	85 (25.1)
Methotrexate only	185 (54.6)
Methotrexate sodium only	24 (7.1)
At Week 52	
No csDMARD ^b	95 (28.0)
Methotrexate only	177 (52.2)
Methotrexate sodium only	25 (7.4)
<p>a. Bimekizumab is only approved in combination with methotrexate and as monotherapy. b. The following drugs were defined as csDMARDs in the BE OPTIMAL study: methotrexate, sulfasalazine, leflunomide, methotrexate sodium, apremilast, ciclosporin, tofacitinib, hydroxychloroquine sulphate, azathioprine.</p> <p>csDMARD: conventional synthetic DMARD; DMARD: disease-modifying antirheumatic drug; n: number of patients with therapy; N: number of analysed patients; RCT: randomized controlled trial</p>	

For the adalimumab arm, the analyses subsequently submitted did not result in any changes compared with the dossier assessment. 97 patients (89.8%) were treated in compliance with the approval.

Accordingly, a total of 378 patients (84.6%) of the subpopulation presented by the company received concomitant csDMARD therapy in compliance with the approval during the course of the study.

Summary

The subpopulation relevant for the benefit assessment comprises only patients who received approval-compliant treatment and for whom it is ensured that there was an insufficient response or intolerance to at least one prior csDMARD therapy. In summary, the data subsequently submitted by the company show that 96.4% of the patients in the presented subpopulation had an inadequate response to at least one csDMARD in compliance with the approval. During the study, 84.6% of patients received monotherapy or an approval-compliant concomitant csDMARD therapy.

This means that at least 362 patients (81%) of the subpopulation presented by the company fulfilled both criteria, with a maximum of 378 (84.6%).

Therefore, the subpopulation of the BE OPTIMAL study presented by the company is used for the benefit assessment.

2.2 Studies included

The study presented in the following table was included in the benefit assessment.

Table 2: Study pool – RCT, direct comparison: bimekizumab vs. adalimumab

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)	CSR (yes/no [citation])	Registry entries ^b (yes/no [citation])	Publication and other sources ^c (yes/no [citation])
PA0010 (BE OPTIMAL ^d)	Yes	Yes	No	Yes [9-11]	Yes [12,13]	Yes [14]

a. Study for which the company was sponsor.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.
CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool for research question 1 of the benefit assessment of bimekizumab in comparison with the appropriate comparator therapy (ACT) coincides with the company's study pool and consists of the BE OPTIMAL study.

2.3 Study characteristics

Detailed characteristics of the BE OPTIMAL study including the relevant subpopulation can be found in dossier assessment A23-60 [1].

Risk of bias across outcomes (study level)

Table 3 shows the risk of bias across outcomes (risk of bias at study level).

Table 3: Risk of bias across outcomes (study level) – RCT, direct comparison: bimekizumab vs. adalimumab

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
BE OPTIMAL	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the study.

2.4 Outcomes included

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

- Mortality
 - all-cause mortality
- Morbidity
 - minimal disease activity (MDA)
 - remission, recorded using the Disease Activity in Psoriatic Arthritis (DAPSA) ≤ 4
 - swollen joint count, recorded using the SJC66
 - tender joint count, recorded using the TJC68
 - enthesitis, recorded using the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index and the Leeds Enthesitis Index (LEI)
 - dactylitis, recorded using the LDI
 - axial involvement, recorded using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
 - skin symptoms, recorded using the Psoriasis Area and Severity Index (PASI)
 - fingernail involvement, recorded using the modified Nail Psoriasis Severity index [mNAPSI])

- arthritis pain, recorded using the Patient Assessment of Arthritis Pain (PtAAP) visual analogue scale (VAS)
- patient global assessment of disease activity (Patient Global Assessment of Psoriatic Arthritis [PGA-PsA] VAS)
- impact of disease, recorded using the 12-item Psoriatic Arthritis Impact of Disease (PsAID-12)
- health status (EQ-5D VAS)
- physical functioning, recorded using the Health Assessment Questionnaire-Disability Index (HAQ-DI)
- fatigue, recorded using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue
- Health-related quality of life
 - Short Form (36) Health Survey (SF-36)
 - Psoriatic Arthritis Quality of Life (PsAQOL)
- Side effects
 - adverse events (AEs), supplementary information
 - serious AEs (SAEs)
 - discontinuation due to AEs
 - infections and infestations (System Organ Class [SOC], AE)
 - fungal infections (High Level Group Term [HLGT], AE)
 - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used additional outcomes in its dossier (Module 4 C).

Table 4 shows the outcomes for which data were available in the included study.

Table 4: Matrix of outcomes – RCT, direct comparison: bimekizumab vs. adalimumab

Study	Outcomes																							
	All-cause mortality ^a	MDA	Remission (DAPSA ≤ 4)	Swollen joint count (SJC66)	Tender joint count (TJC68)	Enthesitis (SPARCC Enthesitis Index)	Enthesitis (LEI)	Dactylitis (LDI)	Axial involvement (BASDAI)	Skin symptoms (PASI)	Fingernail involvement (mNAPSI)	Arthritis pain (PtAAP VAS)	Patient-reported global disease activity (PGA-PsA VAS)	Disease impact (PsAID-12)	Health status (EQ-5D VAS)	Physical functioning (HAQ-DI)	Fatigue (FACIT-Fatigue)	Health-related quality of life (SF-36)	Health-related quality of life (PsaQOL)	SAEs ^b	Discontinuation due to AEs	Infections and infestations (SOC, AEs)	Fungal infections (HLGT, AEs)	Further specific AEs
BE OPTIMAL	Yes	Yes	Yes	Yes	Yes	No ^c	Yes	No ^c	Yes	No ^c	No ^c	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No ^d
<p>a. Operationalized via AEs that led to death.</p> <p>b. Without consideration of the following PTs defined by the company as disease-related events in Module 4 C: guttate psoriasis, nail psoriasis, psoriasis, pustular psoriasis, arthralgia, musculoskeletal stiffness, psoriatic arthropathy, and musculoskeletal pain.</p> <p>c. No suitable data available; see Section 2.5 of the present addendum for reasoning.</p> <p>d. No further specific AEs were identified based on the AEs occurring in the relevant study.</p> <p>AE: adverse event; BASDA: Bath Ankylosing Spondylitis Disease Activity Index; DAPSA: Disease Activity in Psoriatic Arthritis; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ-DI: Health Assessment Questionnaire-Disability Index; HLGT: High Level Group Term; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesitis Index; MDA: minimal disease activity; mNAPSI: modified Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index; NRI: non-responder imputation; PGA-PsA: Patient Global Assessment of Psoriatic Arthritis; PsAID-12: 12-item Psoriatic Arthritis Impact of Disease; PsAQOL: Psoriatic Arthritis Quality of Life; PT: Preferred Term; PtAAP: Patient Assessment of Arthritis Pain; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form 36; SJC: swollen joint count; SOC: System Organ Class; SPARCC: Spondyloarthritis Research Consortium of Canada; VAS: visual analogue scale</p>																								

Not for all outcomes listed in Table 4 did the company's dossier contain suitable data. This is explained below.

Analyses based on a limited study population

As described in the dossier assessment, analyses based on a limited study population – e.g. only patients with disease activity at baseline – are not appropriate. Patients who, for example, do not have enthesitis or only minor skin symptoms at baseline are, in principle, also at risk of developing these symptoms in the further course of the disease. This means that the entire study population or relevant subpopulation was at risk for these outcomes and must therefore be taken into account when analysing these outcomes.

For the following outcomes, the company's dossier presented responder analyses that only included patients with the following disease activity at baseline:

- SPARCC Enthesitis Index: only patients with SPARCC > 0 at baseline
- LEI: only patients with LEI > 0 at baseline
- LDI: only patients with LDI > 0 at baseline
- BASDAI: only patients with a value of > 4 at baseline
- PASI: only patients with psoriasis on $\geq 3\%$ of body surface area (BSA) at baseline
- mNAPSI: only patients with mNAPSI > 0 at baseline
- psAID-12: only patients with a value of > 3 at baseline
- HAQ-DI: only patients with a value of ≥ 0.45 at baseline
- FACIT-F: only patients with a value of ≤ 44.2 at baseline

Under certain circumstances, however, an analysis based on a restricted population can still be suitable for drawing a conclusion for the total target population if its proportion of the target population is large enough. In the present assessment, this applies to the outcomes of BASDAI, FACIT-F and PsAID-12, as $\geq 70\%$ of the relevant subpopulation were included in the analysis.

This is not the case for the other outcomes, as 65.3% of the relevant subpopulation were missing from the responder analysis for the SPARCC Enthesitis Index, 70.2% for the LEI and 89.9% for the LDI. For the HAQ-DI, the proportion of missing patients in the responder analysis was 32.2%. The analyses of PASI (PASI100, PASI90 and PASI75) and mNAPSI (mNAPSI100) did not include 51.0% and 44.7% of the relevant subpopulation respectively. The responder analyses on these outcomes are therefore not suitable for the benefit assessment.

After the oral hearing, the company subsequently submitted analyses based on the entire subpopulation for the outcome of dactylitis, recorded using the LDI. However, this analysis is also not suitable for the benefit assessment (see below).

Further operationalizations are available for the outcome of enthesitis, recorded using the LEI, and for the HAQ-DI. Since the responder analyses for these outcomes are not suitable due to the described restriction of the analysis population, the change at Week 52 compared with baseline is used.

The company also presented analyses of further operationalizations for PASI and mNAPSI, but, in accordance with the study protocol, these outcomes were recorded during the course of the study only in patients who had a certain level of disease activity at baseline (see above). Therefore, no analyses taking into account the entire subpopulation are possible for these outcomes and the analyses presented in the dossier are not suitable for the benefit assessment.

Enthesitis

Two operationalizations (LEI and SPARCC Enthesitis Index) are used for the outcome of enthesitis. The LEI was developed for the therapeutic indication of psoriatic arthritis [15] and the SPARCC Enthesitis Index for the therapeutic indication of spondyloarthritis [16]. In the present benefit assessment, the outcome of enthesitis is therefore assessed in an overall consideration of the operationalizations for both outcomes, but primarily on the basis of the LEI.

Dactylitis

After the oral hearing, the company subsequently submitted responder analyses based on the entire subpopulation for the outcome of dactylitis. However, few patients were included in the analyses with their actually observed values. At Week 52, the proportion of patients whose values were imputed by non-responder imputation (NRI) was about 60%. The company did not give any reasons for the high proportion of imputed values.

It is unclear in how many patients the missing values are due to a change in the protocol for recording the LDI. According to the original protocol (28 November 2018), the recording of the LDI was planned regardless of existing symptoms at baseline. With Protocol Amendment 1 (10 January 2020), the LDI was only recorded in patients with LDI > 0 at baseline. This restriction was withdrawn with Protocol Amendment 2 (22 February 2021).

The analyses of the LDI subsequently submitted are therefore not suitable for the benefit assessment.

Remission (DAPSA \leq 4)

The DAPSA is a validated sum score for assessing disease activity with a focus on the manifestation of peripheral arthritis in patients with psoriatic arthritis [17,18]. It is composed of the components of patient-reported global disease activity (PGA arthritis), arthritis pain (PtAAP), TJC68, SJC66 and the inflammation marker high-sensitivity C-reactive protein (hsCRP).

The DAPSA is an open-ended scale starting at 0, with higher scores reflecting more severe disease activity. A value \leq 4 indicates remission [19].

Patient-reported global disease activity (PGA-PsA VAS)

The PGA-PsA VAS is a self-report instrument for assessing the current global disease activity of psoriatic arthritis [20,21]. On a scale from 0 (very good, no symptoms) to 100 (very bad, severe symptoms), the patients rate how well they feel on the day of recording, taking into account all disease manifestations of psoriatic arthritis and their effects.

In the dossier, the company used the PGA arthritis VAS as an additional operationalization of patient-reported global disease activity [22,23]. The PGA Arthritis VAS was developed for rheumatoid arthritis and records the disease activity exclusively for arthritis and thus only one component of the clinical picture of psoriatic arthritis.

The PGA-PsA VAS is included in the present benefit assessment because this instrument was developed for psoriatic arthritis. The company used post hoc analyses post hoc for the improvement of the PGA-PsA VAS by \geq 15 points. Since the response criterion corresponds to exactly 15% of the scale range, it can be taken into account in accordance with the *General Methods* of the Institute [24].

Disease impact (PsAID-12)

The PsAID-12 is a self-report instrument for determining the impact of disease. It comprises 12 questions on the following items: pain, fatigue, skin problems, ability to work/leisure, functional capacity, feeling of discomfort, sleep disturbance, coping, anxiety, fear and uncertainty, embarrassment and/or shame, social participation, and depression [25]. Each question is answered on a numeric rating scale (NRS) from 0 (best condition) to 10 (worst condition). To calculate the PsAID-12 score, the disease domains are weighted and then averaged. The PsAID-12 total score and the scores of the individual domains can assume values from 0 to 10, with higher values indicating worse condition. The PsAID-12 records the impact within the last week.

The company presented analyses of the improvement by \geq 3 points for the total score and for the individual items.

The improvement in total score by ≥ 3 points is used for this benefit assessment. Since the response criterion was prespecified and corresponds to at least 15% of the scale range, the presented analyses can be taken into account in accordance with the *General Methods* of the Institute [24].

Health-related quality of life (PsAQOL)

The PsAQOL is a self-report instrument for assessing health-related quality of life in patients with psoriatic arthritis [26]. It consists of 20 questions, each of which is answered with yes (1) or no (0). The questionnaire asks about the condition “at the moment”. This results in a total score of 0 to 20, with higher values indicating worse condition.

The improvement in PsAQOL by ≥ 3 points is used for this benefit assessment. The analysis was specified post hoc. Since the response criterion corresponds to exactly 15% of the scale range, it can be taken into account in accordance with the *General Methods* of the Institute [24].

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, only the operationalization of AEs that led to study discontinuation was available in the dossier. With the comments, the company subsequently submitted results on the overall rate of AEs that led to treatment discontinuation. AEs that led to treatment discontinuation are used for the benefit assessment.

However, analyses at Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) level are only available for the operationalization of AEs that led to study discontinuation. Overall, there were only few events (3 events under bimekizumab and 0 under adalimumab) that led to discontinuation of treatment, but not to discontinuation of the study. In the present case, the results at SOC and PT level operationalized as AEs that led to study discontinuation are therefore used instead.

2.5 Risk of bias

Table 5 describes the risk of bias for the results of the relevant outcomes.

Table 5: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: bimekizumab vs. adalimumab

Study	Outcomes																									
	Study level	All-cause mortality ^a	MDA	Remission (DAPSA ≤ 4)	Swollen joint count (SJC66)	Tender joint count (TJC68)	Enthesitis (SPARCC Enthesitis Index)	Enthesitis (LEI)	Dactylitis (LDI)	Axial involvement (BASDAI)	Skin symptoms (PASI)	Fingernail involvement (mNAPSI)	Arthritis pain (PtAAP VAS)	Patient-reported global disease activity (PGA-PsA VAS)	Disease impact (PsAID-12)	Health status (EQ-5D VAS)	Physical functioning (HAQ-DI)	Fatigue (FACIT-Fatigue)	Health-related quality of life (SF-36)	Health-related quality of life (PsAQOL)	SAEs ^b	Discontinuation due to AEs	Infections and infestations (SOC, AEs)	Fungal infections (HLGT, AEs)	Further specific AEs ^c	
BE OPTIMAL	L	L	L	L	L	L	- ^d	L	- ^d	H ^e	- ^d	- ^d	L	L	H ^e	L	L	H ^e	H ^f	L	L	L	L	L	L	-

a. Operationalized via AEs that led to death.
 b. Without consideration of the following PTs defined by the company as disease-related events in Module 4 C: guttate psoriasis, nail psoriasis, psoriasis, pustular psoriasis, arthralgia, musculoskeletal stiffness, psoriatic arthropathy, and musculoskeletal pain.
 c. No further specific AEs were selected.
 d. No suitable data available; see Section 2.4 of the present addendum for reasoning.
 e. Overall high proportion of patients who are either not included in the analysis due to a restriction of the study population or whose values are imputed by NRI.
 f. High proportion of missing values imputed by NRI (> 10%).

AE: adverse event; BASDA: Bath Ankylosing Spondylitis Disease Activity Index; DAPSA: Disease Activity in Psoriatic Arthritis; FACIT: Functional Assessment of Chronic Illness Therapy; H: high; HAQ-DI: Health Assessment Questionnaire-Disability Index; HLGT: High Level Group Term; L: low; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesitis Index; MDA: minimal disease activity; mNAPSI: modified Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index; NRI: non-responder imputation; PGA-PsA: Patient Global Assessment of Psoriatic Arthritis; PsAID-12: 12-item Psoriatic Arthritis Impact of Disease; PsAQOL: Psoriatic Arthritis Quality of Life; PT: Preferred Term; PtAAP: Patient Assessment of Arthritis Pain; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form 36; SJC: swollen joint count; SOC: System Organ Class; SPARCC: Spondyloarthritis Research Consortium of Canada; VAS: visual analogue scale

The risk of bias of the results in the BE OPTIMAL study varies by outcome. It is rated as low for the outcomes of all-cause mortality, MDA, remission (DAPSA \leq 4), swollen joint count (SJC66), tender joint count (TJC68), enthesitis (LEI), arthritis pain (PtAAP-VAS), patient-reported global disease activity (PGA-PsA VAS) health status (EQ-5D VAS), physical functioning (HAQ-DI), and health-related quality of life (PsAQOL). It is also rated as low for each of the outcomes of the category of side effects.

The risk of bias is rated as high for the results of the outcomes of axial involvement (BASDAI), disease impact (PsAID-12), fatigue (FACIT-Fatigue), and health-related quality of life (SF-36). For results on health-related quality of life (SF-36), the high risk of bias is due to a high proportion (> 10%) of missing values imputed by NRI. The high risk of bias for the results of the outcomes of axial involvement (BASDAI), fatigue (FACIT-Fatigue) and disease impact (PsAID-12) is due to the fact that, as described in Section 2.4, the analyses are based on a limited study population, which is why a high proportion of patients were not included in the analysis at all, and at the same time, values were imputed by NRI for some patients.

2.6 Results

Table 6 and Table 7 summarize the results of the comparison of bimekizumab versus adalimumab in bDMARD-naive patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior DMARD therapy. Where necessary, calculations conducted by the Institute supplement the data from the company's dossier and commenting procedure.

Tables on common AEs, SAEs, and discontinuations due to AEs are presented in Appendix A.

Table 6: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: bimekizumab vs. adalimumab (multipage table)

Study Outcome category Outcome Time point	Bimekizumab		Adalimumab		Bimekizumab vs. adalimumab RR [95% CI]; p-value ^a
	N	Patients with event n (%)	N	Patients with event n (%)	
BE OPTIMAL					
Mortality					
All-cause mortality ^b	339	0 (0)	108	0 (0)	–
Morbidity^c					
MDA ^d	339	181 (53.4)	108	59 (54.6)	1.00 [0.82; 1.22]; 0.975
Remission (DAPSA \leq 4) ^e	339	78 (23.0)	108	32 (29.6)	0.79 [0.56; 1.12]; 0.189
Tender joints (TJC68 \leq 1)	339	157 (46.3)	108	52 (48.1)	0.97 [0.78; 1.22]; 0.825

Table 6: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: bimekizumab vs. adalimumab (multipage table)

Study Outcome category Outcome Time point	Bimekizumab		Adalimumab		Bimekizumab vs. adalimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value ^a
Swollen joints (SJC66 ≤ 1)	339	241 (71.1)	108	72 (66.7)	1.09 [0.95; 1.26]; 0.227
Enthesitis (SPARCC Enthesitis Index = 0)				No suitable data	
Dactylitis (LDI = 0)				No suitable data	
Axial involvement (BASDAI; improvement by ≥ 1.5 points) ^f	243	175 (72.0)	83	60 (72.3)	1.00 [0.86; 1.17]; 0.984
Skin symptoms (PASI)				No suitable data	
Fingernail involvement (mNAPSI)				No suitable data	
Arthritis pain (PtAAP VAS, improvement by ≥ 15 points) ^g	339	215 (63.4)	108	69 (63.9)	1.00 [0.85; 1.18]; 0.992
Disease activity (PGA-PsA VAS; improvement by ≥ 15 points) ^g	339	228 (67.3)	108	72 (66.7)	1.02 [0.88; 1.19]; 0.811
Disease impact (PsAID-12, improvement by ≥ 3 points) ^h	230	113 (49.1)	86	42 (48.8)	1.02 [0.79; 1.32]; 0.864
Health status (EQ-5D VAS; improvement by ≥ 15 points) ⁱ	339	158 (46.6)	108	54 (50.0)	0.95 [0.76; 1.18]; 0.642
Fatigue (FACIT-Fatigue, improvement by ≥ 7.8 points) ^j	246	110 (44.7)	91	35 (38.5)	1.17 [0.87; 1.57]; 0.302
Health-related quality of life^c					
SF-36					
MCS (improvement by ≥ 9.6 points [15%]) ^k	339	29 (8.6)	108	11 (10.2)	0.84 [0.43; 1.62]; 0.604
PCS (improvement by ≥ 9.4 points [15%]) ^l	339	105 (31.0)	108	42 (38.9)	0.82 [0.62; 1.08]; 0.152
PsAQOL (improvement by ≥ 3 points) ^m	339	128 (37.8)	108	46 (42.6)	0.89 [0.69; 1.15]; 0.384
Side effects					
AEs ⁿ	339	284 (83.8)	108	83 (76.9)	
SAEs ⁿ	339	22 (6.5)	108	8 (7.4)	0.87 [0.40; 1.89]; 0.721
Discontinuation due to AEs ^o	339	12 (3.5)	108	6 (5.6)	0.61 [0.24; 1.59]; 0.311
Infections and infestations (SOC, AEs)	339	184 (54.3)	108	43 (39.8)	1.36 [1.06; 1.75]; 0.017
Fungal infections (HLGT, AEs)	339	44 (13.0)	108	2 (1.9)	7.01 [1.73; 28.43]; 0.006

Table 6: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: bimekizumab vs. adalimumab (multipage table)

Study Outcome category Outcome Time point	Bimekizumab		Adalimumab		Bimekizumab vs. adalimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value ^a
<p>a. Effect estimate and p-value from a logistic regression, stratified by region; for morbidity outcomes and health-related quality of life outcomes additionally adjusted for the baseline value.</p> <p>b. Operationalized via AEs that led to death.</p> <p>c. Missing values were imputed using NRI.</p> <p>d. For classification as an MDA responder, 5 of the following 7 criteria must be met: TJC68 \leq 1; SJC66 \leq 1; PASI \leq 1 (for patients with BSA \geq 3 at baseline) or BSA \leq 3, PtAAP VAS \leq 15; PGA-PsA VAS \leq 20, HAQ-DI \leq 0.5 and LEI \leq 1.</p> <p>e. The DAPSA scale starts at 0 and is open-ended. A higher value reflects higher disease activity. A DAPSA \leq 4 indicates remission.</p> <p>f. Proportion of patients with a score decrease by \geq 1.5 points from baseline to Week 52, at a scale range of 0 to 10. Lower (decreasing) values indicate an improvement in symptoms. Analysis refers to patients with a BASDAI \geq 4 at baseline.</p> <p>g. Proportion of patients with a score decrease by \geq 15 points from baseline to Week 52, at a scale range of 0 to 100. Lower (decreasing) values indicate an improvement in symptoms.</p> <p>h. Proportion of patients with a score decrease by \geq 3 points from baseline to Week 52, at a scale range of 0 to 10. Lower (decreasing) values indicate an improvement in symptoms. Analysis refers to patients with a PsAID-12 \geq 3 at baseline.</p> <p>i. Proportion of patients with a score increase by \geq 15 points from baseline to Week 52, at a scale range of 0 to 100. Higher (increasing) values indicate an improvement in symptoms.</p> <p>j. Proportion of patients with a score increase by \geq 7.8 points from baseline to Week 52, at a scale range of 0 to 52. Higher (increasing) values indicate an improvement in symptoms. Analysis refers to patients with a FACIT-F \leq 44.2 at baseline.</p> <p>k. Proportion of patients with improvement: increase in MCS score by \geq 9.6 points from baseline to Week 52 (corresponds to 15% of the scale range; normalized scale with a minimum of approx. 6 and a maximum of approx. 70).</p> <p>l. Proportion of patients with improvement: increase in PCS score by \geq 9.4 points from baseline to Week 52 (corresponds to 15% of the scale range; normalized scale with a minimum of approx. 7 and a maximum of approx. 70).</p> <p>m. Proportion of patients with a score decrease by \geq 3 points from baseline to Week 52, at a scale range of 0 to 20. Lower (decreasing) values indicate an improvement in symptoms.</p> <p>n. Without consideration of the following PTs defined by the company as disease-related events in Module 4 C: guttate psoriasis, nail psoriasis, psoriasis, pustular psoriasis, arthralgia, musculoskeletal stiffness, psoriatic arthropathy, and musculoskeletal pain.</p> <p>o. Operationalized via AEs that led to treatment discontinuation.</p> <p>AE: adverse event; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BSA: body surface area; CI: confidence interval; DAPSA: Disease Activity in Psoriatic Arthritis; FACIT: Functional Assessment of Chronic Illness Therapy; HLG: High Level Group Term; LDI: Leeds Dactylitis Index; MCS: Mental Component Summary; MDA: minimal disease activity; mNAPSI: modified Nail Psoriasis Severity Index; n: number of patients with (at least one) event; N: number of analysed patients; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PCS: Physical Component Summary; PGA-PsA: Patient Global Assessment of Arthritis; PsAID-12: 12-item Psoriatic Arthritis Impact of Disease; PsAQOL: Psoriatic Arthritis Quality of Life; PtAAP: Patient Assessment of Arthritis Pain; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36: Short Form 36 Health Survey; SJC66: swollen joint count 66; SOC: System Organ Class; SPARCC: Spondyloarthritis Research Consortium of Canada; TJC68: tender joint count 68; VAS: visual analogue scale</p>					

Table 7: Results (morbidity, continuous) – RCT, direct comparison: bimekizumab vs. adalimumab

Study Outcome category Outcome	Bimekizumab			Adalimumab			Bimekizumab vs. adalimumab MD [95% CI]; p-value ^b
	N ^a	Values at baseline mean (SD)	Mean change at Week 52 mean ^b (SD)	N ^a	Values at baseline mean (SD)	Mean change at Week 52 mean ^b (SD)	
BE OPTIMAL							
Morbidity							
Enthesitis (LEI) ^c	ND	0.80 (1.4)	-0.34 (0.1)	ND	0.51 (1.2)	-0.23 (0.1)	-0.11 [-0.31; 0.09]; 0.280
Physical functioning (HAQ-DI) ^d	ND	0.81 (0.60)	-0.34 (0.03)	ND	0.88 (0.54)	-0.41 (0.05)	0.07 [-0.03; 0.17]; 0.194
<p>a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.</p> <p>b. MMRM analysis.</p> <p>c. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention (scale range of 0 to 6).</p> <p>d. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention (scale range of 0 to 3).</p> <p>CI: confidence interval; HAQ-DI: Health Assessment Questionnaire-Disability Index; LEI: Leeds Enthesitis Index; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation</p>							

On the basis of the available information, at most hints, for example of an added benefit, can be determined for the outcomes of axial involvement (BASDAI), disease impact (PsAID-12), fatigue (FACIT-F) and health-related quality of life (SF-36) due to the high risk of bias. For the other outcomes for which suitable analyses are available, no more than indications can be derived.

Mortality

All-cause mortality

No patients died in the BE OPTIMAL study. There is no hint of added benefit of bimekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Morbidity

Minimal disease activity

Responder analyses were used for the outcome of MDA. No statistically significant difference between bimekizumab and adalimumab was found. There is no hint of added benefit of bimekizumab versus adalimumab; an added benefit is therefore not proven.

Remission (DAPSA \leq 4)

Responder analyses were used for the outcome of remission (DAPSA \leq 4). No statistically significant difference between bimekizumab and adalimumab was found. There is no hint of added benefit of bimekizumab versus adalimumab; an added benefit is therefore not proven.

Tender joints (TJC68 \leq 1)

Responder analyses were used for the outcome of TJC68. No statistically significant difference between treatment groups was found. There is no hint of added benefit of bimekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Swollen joints (SJC66 \leq 1)

Responder analyses were used for the outcome of SJC66. No statistically significant difference between treatment groups was found. There is no hint of added benefit of bimekizumab in comparison with adalimumab; an added benefit is therefore not proven.

Enthesitis

Enthesitis is operationalized using the LEI and SPARCC Enthesitis Index. The assessment is primarily based on the LEI.

For enthesitis, recorded using LEI, the mean change at Week 52 is used. No statistically significant difference between bimekizumab and adalimumab was found. No suitable data are available for enthesitis recorded using the SPARCC Enthesitis Index. There is overall no hint of added benefit of bimekizumab versus adalimumab; an added benefit is therefore not proven.

Axial involvement (BASDAI)

Responder analyses were used for the outcome of axial involvement (BASDAI). No statistically significant difference between bimekizumab and adalimumab was found. There is no hint of added benefit of bimekizumab versus adalimumab; an added benefit is therefore not proven.

Arthritis pain (PtAAP VAS)

Responder analyses were used for the outcome of arthritis pain (PtAAP VAS). No statistically significant difference between bimekizumab and adalimumab was found. There is no hint of added benefit of bimekizumab versus adalimumab; an added benefit is therefore not proven.

Patient-reported global disease activity (PGA-PsA VAS)

Responder analyses were used for the outcome of patient-reported global disease activity (PGA-PsA VAS). No statistically significant difference between bimekizumab and adalimumab was found. There is no hint of added benefit of bimekizumab versus adalimumab; an added benefit is therefore not proven.

Disease impact (PsAID-12)

Responder analyses were used for the outcome of disease impact (PsAID-12). No statistically significant difference between bimekizumab and adalimumab was found. There is no hint of added benefit of bimekizumab versus adalimumab; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

Responder analyses were used for the outcome of health status (EQ-5D VAS). No statistically significant difference between bimekizumab and adalimumab was found. There is no hint of added benefit of bimekizumab versus adalimumab; an added benefit is therefore not proven.

Physical functioning (HAQ-DI)

The mean change at Week 52 was used for the outcome of physical functioning (HAQ-DI). No statistically significant difference between bimekizumab and adalimumab was found. There is no hint of added benefit of bimekizumab versus adalimumab; an added benefit is therefore not proven.

Fatigue (FACIT-Fatigue)

Responder analyses were used for the outcome of fatigue (FACIT-Fatigue). No statistically significant difference between bimekizumab and adalimumab was found. There is no hint of added benefit of bimekizumab versus adalimumab; an added benefit is therefore not proven.

Other morbidity outcomes

No suitable data are available for the outcomes of dactylitis (LDI), skin symptoms (PASI) and fingernail involvement (mNAPSI). In each case, there is no hint of added benefit of bimekizumab in comparison with adalimumab; an added benefit is therefore not proven for these outcomes.

Health-related quality of life

SF-36

Responder analyses were used for health-related quality of life recorded using the SF-36. No statistically significant difference between bimekizumab and adalimumab was found for either the mental or the physical sum score. There is no hint of added benefit of bimekizumab versus adalimumab; an added benefit is therefore not proven.

PsAQOL

Responder analyses were used for health-related quality of life recorded using the PsAQOL. No statistically significant difference between bimekizumab and adalimumab was found. There is no hint of added benefit of bimekizumab versus adalimumab; an added benefit is therefore not proven.

Side effects

Overall rates of SAEs and discontinuation due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs. There is no hint of greater or lesser harm from bimekizumab in comparison with adalimumab for either of them; greater or lesser harm is therefore not proven.

Infections and infestations (SOC, AE)

A statistically significant difference between treatment groups was found for the outcome of infections and infestations (SOC, AE). This difference was no more than marginal, however. There is no hint of greater or lesser harm from bimekizumab in comparison with adalimumab; greater or lesser harm is therefore not proven.

Fungal infections (HLGT, AE)

For the outcome of fungal infections (HLGT, AE), a statistically significant difference was found to the disadvantage of bimekizumab versus adalimumab. There is an indication of greater harm from bimekizumab in comparison with adalimumab.

2.6.1 Subgroups and other effect modifiers

The following subgroup characteristics were considered for the present benefit assessment:

- age (< 45 years versus ≥ 45 years)
- sex (male versus female)

No suitable characteristic is available for disease severity.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup. Subgroup results where the extent does not differ between subgroups are not presented.

It is not clear from the information provided by the company in the dossier which effect measure was used to calculate the subgroup analyses. For the benefit assessment, the Institute therefore conducted its own calculations based on the relative risk to check the results of the company.

There was no statistically significant interaction for any of the included outcomes. Subgroup results are therefore not presented.

2.7 Probability and extent of the added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [24].

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.

2.7.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.6 (see Table 8).

Table 8: Extent of added benefit at outcome level: bimekizumab vs. adalimumab (multipage table)

Outcome category Outcome Effect modifier Subgroup	Bimekizumab vs. adalimumab Proportion of events (%) or mean change in the course of the study Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser/added benefit not proven
Morbidity		
MDA	53.4% vs. 54.6% RR: 1.00 [0.82; 1.22] p = 0.975	Lesser/added benefit not proven
Remission (DAPSA ≤ 4)	23.0% vs. 29.6% RR: 0.79 [0.56; 1.12] p = 0.189	Lesser/added benefit not proven
Tender joints (TJC68 ≤ 1)	46.3% vs. 48.1% RR: 0.97 [0.78; 1.22] p = 0.825	Lesser/added benefit not proven
Swollen joints (SJC66 ≤ 1)	71.1% vs. 66.7% RR: 1.09 [0.95; 1.26] p = 0.227	Lesser/added benefit not proven
Enthesitis (LEI)	–0.34 vs. –0.23 MD: –0.11 [–0.31; 0.09]; p = 0.280	Lesser/added benefit not proven

Table 8: Extent of added benefit at outcome level: bimekizumab vs. adalimumab (multipage table)

Outcome category Outcome Effect modifier Subgroup	Bimekizumab vs. adalimumab Proportion of events (%) or mean change in the course of the study Effect estimation [95% CI]; p-value Probability^a	Derivation of extent^b
Dactylitis (LDI = 0)	No suitable data	Lesser/added benefit not proven
Axial involvement (BASDAI; improvement by ≥ 1.5 points)	72.0% vs. 72.3% RR: 1.00 [0.86; 1.17]; p = 0.984	Lesser/added benefit not proven
Skin symptoms (PASI)	No suitable data	Lesser/added benefit not proven
Fingernail involvement (mNAPSI)	No suitable data	Lesser/added benefit not proven
Arthritis pain (PtAAP VAS, improvement by ≥ 15 points)	63.4% vs. 63.9% RR: 1.00 [0.85; 1.18] p = 0.992	Lesser/added benefit not proven
Disease activity (PGA-PsA VAS; improvement by ≥ 15 points)	67.3% vs. 66.7% RR: 1.02 [0.88; 1.19] p = 0.811	Lesser/added benefit not proven
Disease impact (PsAID-12, improvement by ≥ 3 points)	49.1% vs. 48.8% RR: 1.02 [0.79; 1.32]; p = 0.864	Lesser/added benefit not proven
Health status (EQ-5D VAS; improvement by ≥ 15 points)	46.6% vs. 50.0% RR: 0.95 [0.76; 1.18]; p = 0.642	Lesser/added benefit not proven
Physical functioning (HAQ-DI)	-0.34 vs. -0.41 MD: -0.07 [-0.03; 0.17]; p = 0.194	Lesser/added benefit not proven
Fatigue (FACIT-Fatigue, improvement by ≥ 7.8 points)	44.7% vs. 38.5% RR: 1.17 [0.87; 1.57]; p = 0.302	Lesser/added benefit not proven
Health-related quality of life		
SF-36 MCS (improvement by ≥ 9.6 points)	8.6% vs. 10.2% RR: 0.84 [0.43; 1.62]; p = 0.604	Lesser/added benefit not proven
PCS (improvement by ≥ 9.4 points)	31.0% vs. 38.9% RR: 0.82 [0.62; 1.08]; p = 0.152	Lesser/added benefit not proven
PsAQOL (improvement by ≥ 3 points)	37.8% vs. 42.6% RR: 0.89 [0.69; 1.15]; p = 0.384	Lesser/added benefit not proven

Table 8: Extent of added benefit at outcome level: bimekizumab vs. adalimumab (multipage table)

Outcome category Outcome Effect modifier Subgroup	Bimekizumab vs. adalimumab Proportion of events (%) or mean change in the course of the study Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
Side effects		
SAEs (without disease-related events)	6.5% vs. 7.4% RR: 0.87 [0.40; 1.89]; p = 0.721	Greater/lesser harm not proven
Discontinuation due to AEs	3.5% vs. 5.6% RR: 0.61 [0.24; 1.59]; p = 0.311	Greater/lesser harm not proven
Infections and infestations (SOC, AEs)	54.3% vs. 39.8% RR: 1.36 [1.06; 1.75] RR: 0.74 [0.57; 0.94] ^c p = 0.017	Greater/lesser harm not proven ^d
Fungal infections (HLGT, AEs)	13.0% vs. 1.9% RR: 7.01 [1.73; 28.43] RR: 0.14 [0.04; 0.58] ^c p = 0.006 Probability: “indication”	Outcome category: non-serious/non-severe side effects CI _u < 0.80 Greater harm; extent: “considerable”
<p>a. Probability provided if there is a statistically significant and relevant effect.</p> <p>b. Depending on the outcome category, estimations of effect size and the scale of the outcome are made with different limits based on the upper limit of the confidence interval (CI_u).</p> <p>c. Institute’s calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.</p> <p>d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.</p> <p>AE: adverse event; BASDA: Bath Ankylosing Spondylitis Disease Activity Index; CI: confidence interval; CI_u: upper limit of confidence interval; DAPSA: Disease Activity in Psoriatic Arthritis; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ-DI: Health Assessment Questionnaire-Disability Index; HLGT: High Level Group Term; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesitis Index; MCS: Mental Component Summary; MD: mean difference; MDA: minimal disease activity; mNAPSI: modified Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index; PCS: Physical Component Summary; PGA-PsA: Patient Global Assessment of Psoriatic Arthritis; PsAID-12: 12-item Psoriatic Arthritis Impact of Disease; PsAQOL: Psoriatic Arthritis Quality of Life; PtAAP: Patient Assessment of Arthritis Pain; RR: relative risk; SAE: serious adverse event; SF-36: Short Form 36 Health Survey; SJC66: swollen joint count 66; SOC: System Organ Class; SPARCC: Spondyloarthritis Research Consortium of Canada; TJC68: tender joint count 68; VAS: visual analogue scale</p>		

2.7.2 Overall conclusion on added benefit

Table 9 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 9: Positive and negative effects from the assessment of bimekizumab in comparison with adalimumab

Positive effects	Negative effects
–	Non-serious/non-severe side effects <ul style="list-style-type: none"> ▪ Fungal infections (HLGT, AE): indication of greater harm – extent: “considerable”
No suitable data are available for the outcomes of dactylitis (LDI), skin involvement (PASI) and fingernail involvement (mNAPSI).	
AE: adverse event; HLGT: High Level Group Term; LDI: Leeds Dactylitis Index; mNAPSI: modified Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index	

Overall, there is an indication of greater harm with considerable extent for bimekizumab compared with adalimumab for the outcome of fungal infections (HLGT, AE). There are no positive effects. In summary, there is no hint of added benefit of bimekizumab in comparison with adalimumab for adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior DMARD therapy; an added benefit of is therefore not proven.

2.8 Summary

As a result of the data subsequently submitted by the company in the commenting procedure, it is possible to use the subpopulation of the BE OPTIMAL study presented by the company for research question 1 (bDMARD-naive patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior DMARD therapy) of the benefit assessment. However, this does not change the conclusion on the added benefit of bimekizumab from dossier assessment A23-60 for research question 1.

For research question 2 (patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior bDMARD therapy), there is no change in comparison with dossier assessment A23-60.

The following Table 10 shows the result of the benefit assessment of bimekizumab under consideration of dossier assessment A23-60 and the present addendum.

Table 10: Bimekizumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT ^a	Probability and extent of added benefit
1	Adults with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior disease-modifying antirheumatic drug (DMARD) therapy ^b	A TNF-alpha antagonist (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an interleukin inhibitor (ixekizumab or secukinumab or ustekinumab), if applicable in combination with methotrexate	Added benefit not proven
2	Adults with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior therapy with biologic disease-modifying antirheumatic drugs (bDMARDs)	Switch to another bDMARD (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab or ustekinumab), if applicable in combination with methotrexate	Added benefit not proven
<p>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.</p> <p>b. The patient population considered for research question 1 consists of bDMARD-naive patients.</p> <p>ACT: appropriate comparator therapy; bDMARD: biologic DMARD; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; TNF: tumour necrosis factor</p>			

The G-BA decides on the added benefit.

3 References

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Appendix A Results on side effects

For the overall rates of AEs and SAEs, the tables below present events for MedDRA SOCs and PTs, each on the basis of the following criteria:

- overall rate of AEs (irrespective of severity): events that occurred in at least 10% of patients in one study arm
- overall rates of SAEs: events that occurred in at least 5% of patients in one study arm
- in addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 11: Common AEs^a – RCT, direct comparison: bimekizumab vs. adalimumab

Study SOC ^b PT ^b	Patients with event n (%)	
	Bimekizumab N = 339	Adalimumab N = 108
BE OPTIMAL		
Overall AE rate	287 (84.7)	85 (78.7)
General disorders and administration site conditions	34 (10.0)	16 (14.8)
Respiratory, thoracic and mediastinal disorders	30 (8.8)	8 (7.4)
Oropharyngeal pain	10 (2.9)	2 (1.9)
Skin and subcutaneous tissue disorders	55 (16.2)	16 (14.8)
Blood and lymphatic system disorders	25 (7.4)	4 (3.7)
Leukopenia	11 (3.2)	3 (2.8)
Gastrointestinal disorders	71 (20.9)	14 (13.0)
Diarrhoea	19 (5.6)	4 (3.7)
Nausea	13 (3.8)	6 (5.6)
Nervous system disorders	40 (11.8)	14 (13.0)
Headache	22 (6.5)	5 (4.6)
Vascular disorders	21 (6.2)	6 (5.6)
Hypertension	15 (4.4)	5 (4.6)
Cardiac disorders	10 (2.9)	0 (0)
Infections and infestations	184 (54.3)	43 (39.8)
Bronchitis	10 (2.9)	2 (1.9)
Urinary tract infection	22 (6.5)	4 (3.7)
Upper respiratory tract infection	34 (10.0)	7 (6.5)
Nasopharyngitis	42 (12.4)	6 (5.6)
Oral candidiasis	17 (5.0)	1 (0.9)
Pharyngitis	19 (5.6)	3 (2.8)
Hepatobiliary disorders	14 (4.1)	2 (1.9)
Psychiatric disorders	14 (4.1)	4 (3.7)
Musculoskeletal and connective tissue disorders	64 (18.9)	22 (20.4)
Arthralgia	14 (4.1)	3 (2.8)
Back pain	18 (5.3)	5 (4.6)
Metabolism and nutrition disorders	28 (8.3)	10 (9.3)
Investigations	48 (14.2)	21 (19.4)
Injury, poisoning and procedural complications	40 (11.8)	10 (9.3)
a. Events that occurred in ≥ 10 patients in at least one study arm.		
b. MedDRA version 19.0; SOC and PT notation taken from Module 4 C.		
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		

Table 12: Common SAEs^a – RCT, direct comparison: bimekizumab vs. adalimumab

Study SOC ^b PT ^b	Patients with event n (%)	
	Bimekizumab N = 339	Adalimumab N = 108
BE OPTIMAL		
Overall SAE rate^c	22 (6.5)	8 (7.4)
<p>a. Events that occurred in ≥ 10 patients and in $\geq 1\%$ of patients in the bimekizumab arm and in $\geq 5\%$ of patients in the adalimumab arm.</p> <p>b. MedDRA version 19.0; SOC and PT notation taken from Module 4 C.</p> <p>c. At the MedDRA SOC/PT level, no SOCs and PTs in the bimekizumab arm and in the adalimumab arm met the criterion for presentation.</p> <p>MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class</p>		

Table 13: Discontinuation due to AEs – RCT, direct comparison: bimekizumab vs. adalimumab

Study SOC ^b PT ^b	Patients with event n (%)	
	Bimekizumab N = 339	Adalimumab N = 108
BE OPTIMAL		
Overall rate of discontinuations due to AEs	9 (2.7)	6 (5.6)
General disorders and administration site conditions	0 (0)	2 (1.9)
Drug intolerance	0 (0)	1 (0.9)
Fatigue	0 (0)	1 (0.9)
Skin and subcutaneous tissue disorders	2 (0.6)	2 (1.9)
Rash	0 (0)	1 (0.9)
Rash maculo-papular	1 (0.3)	0 (0)
Pustular psoriasis	0 (0)	1 (0.9)
Toxic skin eruption	1 (0.3)	0 (0)
Blood and lymphatic system disorders	1 (0.3)	1 (0.9)
Leukopenia	1 (0.3)	0 (0)
Thrombocytopenia	0 (0)	1 (0.9)
Infections and infestations	2 (0.6)	0 (0)
Arthritis bacterial	1 (0.3)	0 (0)
Staphylococcal skin infection	1 (0.3)	0 (0)
Hepatobiliary disorders	1 (0.3)	1 (0.9)
Drug-induced liver injury	1 (0.3)	0 (0)
Non-alcohol steatohepatitis	0 (0)	1 (0.9)
Psychiatric disorders	1 (0.3)	0 (0)
Anxiety	1 (0.3)	0 (0)
Musculoskeletal and connective tissue disorders	0 (0)	1 (0.9)
Psoriatic arthropathy	0 (0)	1 (0.9)
Investigations	2 (0.6)	0 (0)
Blood bilirubin increased	1 (0.3)	0 (0)
Hepatic enzyme increased	1 (0.3)	0 (0)
a. Operationalized via AEs that led to study discontinuation. There were only few events that led to discontinuation of therapy but not to discontinuation of the study (3 in the bimekizumab arm and 0 in the adalimumab arm).		
b. MedDRA version 19.0; SOC and PT notation taken from Module 4 C.		
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		