Bimekizumab (psoriatic arthritis)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent and the German Psoriasis Association (Deutscher Psoriasis Bund) for participating in the written exchange and for their support. The respondent and the German Psoriasis Association were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ACR50	50% improvement im American College of Rheumatology criteria
ACT	appropriate comparator therapy
AE	adverse event
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD	biologic disease-modifying antirheumatic drug
BSA	body surface area
CASPAR	Classification Criteria for the Diagnosis of Psoriatic Arthritis
csDMARD	conventional synthetic disease-modifying antirheumatic drug
DLQI	Dermatology Life Quality Index
DMARD	disease-modifying antirheumatic drug
eCRF	electronic case report form
EMA	European Medicines Agency
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health Assessment Questionnaire-Disability Index
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDI	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index
mNAPSI	modified Nail Psoriasis Severity Index
NSAID	nonsteroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
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
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPARCC	Spondyloarthritis Research Consortium of Canada
SPC	Summary of Product Characteristics

I 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 3 July 2023.

Research question

The aim of the present report is to assess the added benefit of bimekizumab, alone or in combination with methotrexate, in comparison with the appropriate comparator therapy (ACT) in adult patients with active psoriatic arthritis if response to prior therapy with disease-modifying antirheumatic drugs (DMARDs) was inadequate or this therapy was not tolerated.

The research questions shown in Table 2 are derived from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of bimekizumab

Research question	Therapeutic indication	ACT[a]
1	Adults with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior DMARD[b] therapy[c]	A TNF-alpha antagonist (**adalimumab** or certolizumab pegol or etanercept or golimumab or infliximab) or an interleukin inhibitor (ixekizumab or secukinumab or ustekinumab), if applicable in combination with methotrexate
2	Adults with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior therapy with 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

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**.
b. This refers to csDMARDs.
c. The patient population considered for research question 1 consists of bDMARD-naive patients.

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

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

- Research question 1: biologic disease-modifying antirheumatic drug (bDMARD)-naive patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior DMARD therapy
- Research question 2: patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior bDMARD therapy

The company followed the specification of the ACT for both research questions. For research question 1, the company chose adalimumab from the specified options. For research question 2, the company did not choose a drug from the named options and did not include any studies, either.

The assessment is 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: bDMARD-naive patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior DMARD therapy

Results

The company identified the BE OPTIMAL study for the direct comparison of bimekizumab versus adalimumab and used a subpopulation, which it considered to be a relevant, for the benefit assessment. The BE OPTIMAL study is a double-blind RCT, which compared bimekizumab with adalimumab. The duration of treatment with the study medication was 52 weeks. A total of 852 patients were randomized in a ratio of 3:2:1 to treatment with bimekizumab (N = 431), placebo (N = 281) and adalimumab (N = 140). After Week 16, patients in the placebo arm were switched to treatment with bimekizumab until Week 52. This placebo arm is not relevant for the benefit assessment and is no longer considered hereinafter.

The study population included adult patients who had active psoriatic arthritis, defined according to the Classification Criteria for Psoriatic Arthritis (CASPAR), for at least 6 months. Patients had to have ≥ 3 swollen and ≥ 3 tender joints and active plaque psoriasis or a documented history of plaque psoriasis. In addition, the patients had to be bDMARD-naive.

The dosage of bimekizumab for patients in the intervention arm was predominantly in compliance with the Summary of Product Characteristics (SPC). The dosage of adalimumab was in compliance with the approval. Under defined conditions, treatment with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, analgesics and oral corticosteroids initiated before study start could be continued during treatment with the study medication. In patients with no response to therapy at Week 16, the concomitant therapy could be adjusted from this point onwards.

The primary outcome of the study was the response according to American College of Rheumatology (ACR) criteria with at least 50% improvement at Week 16 (ACR50). Patient-relevant outcomes on morbidity, health-related quality of life and side effects were also recorded.

The company presented analyses at Week 24 and Week 52 (final analysis).

Suitability of the subpopulation presented by the company for research question 1 is unclear

The approval of bimekizumab is restricted to patients who have had an inadequate response or who have been intolerant to one or more DMARDs. Research question 1 comprises pretreated patients who are bDMARD-naive, i.e. who have only received pretreatment with at least one csDMARD. However, pretreatment with a csDMARD was not an inclusion criterion in the BE OPTIMAL study. For this reason, the company only used the subpopulation with at least one prior csDMARD therapy who, according to the company, had had an inadequate response or who had been intolerant to csDMARD therapy, for the benefit assessment. Prior therapy includes both therapy that was ongoing at the time of study inclusion and previously completed therapy with csDMARDs. The subpopulation comprises 339 patients in the bimekizumab arm and 108 patients in the adalimumab arm. The subpopulation is not used for the benefit assessment. This is justified below.

Inadequate response to prior therapy with a csDMARD

The company did not provide any specific information on its definition of an inadequate response. In the BE OPTIMAL study, approximately 80% of the presented subpopulation in both study arms had been pretreated with only one csDMARD prior to inclusion in the study. Since the proportion of patients with concomitant csDMARD therapy at baseline was about 90%, it can be assumed that most of them were continuing their only previous therapy at this time. The duration of pretreatment with a csDMARD is important for assessing whether patients with only one prior csDMARD therapy, which was continued at baseline, had an inadequate response because guidelines recommend to escalate therapy after a treatment duration of 12 weeks to 6 months if response is inadequate. The company did not provide any information on the duration of pretreatment, but a minimum duration of treatment can be inferred for some of these patients based on the inclusion criteria. Parallel administration of methotrexate was only permitted if it had been started at least 12 weeks before baseline and had been given at a stable dose for at least 8 weeks before randomization. A total of 74.7% of patients received methotrexate at baseline and thus had at least 12 weeks of pretreatment with a csDMARD. Based on the guideline recommendations, 12 weeks is the minimum treatment duration after which therapy can be escalated if the response is insufficient. However, it is unclear whether the treatment duration of 12 weeks was actually long enough in all patients to determine a lack of response to treatment.

10.5% of all patients in the subpopulation had already discontinued a previous csDMARD therapy before baseline. In this case, the reasons for discontinuation (primary lack of response, secondary lack of response, intolerance, partial response, other) had to be recorded in the electronic case report form (eCRF). However, these data were not provided by the company. It therefore remains uncertain whether and to what extent there were reasons other than an inadequate response or intolerance for the discontinuation of treatment.

The inclusion criterion of suitability for treatment with adalimumab per local approval is also not suitable to ensure that at least 80% of the patients in the subpopulation presented by the company had had an inadequate response or had been intolerant to prior csDMARD therapy. For example, not in all countries where the BE OPTIMAL study was conducted, does the local approval of adalimumab necessarily include patients with an inadequate response to prior csDMARD therapy, concurring with the approval of bimekizumab. Information on the number of patients included in the BE OPTIMAL study in the individual countries is only available for the total population. According to this, at least 75.5% of patients in the total population had an inadequate response to previous csDMARD therapy at the time of study inclusion. However, it is unclear how high the proportion of patients is in the subpopulation presented.

Based on the uncertainties described, it is not sufficiently ensured that the criterion of insufficient response or intolerance is fulfilled in at least 80% of the patients in the subpopulation presented by the company.

Use of csDMARDs was partly not in compliance with the approval

According to the SPC, bimekizumab is approved as monotherapy or in combination with methotrexate. In the BE OPTIMAL study, 252 of the patients (74.3%) in the bimekizumab arm received methotrexate at baseline, 49 (14.5%) received a csDMARD other than methotrexate, and 38 (11.2%) received no csDMARD at all. Based on this information, it can initially be assumed that treatment with bimekizumab was initiated at the start of the study in up to 290 of the patients (85.5%) in compliance with the approval. However, it was possible to adjust the csDMARD therapy during the course of the study as so-called rescue therapy and, in principle, to administer several csDMARDs in parallel. Thus, it cannot be ruled out that some of the patients who received concomitant treatment with methotrexate at the start of the study also received another csDMARD not covered by the approval. Based on the information on baseline and concomitant therapy, however, the proportion was not higher than 5.3%. This means that at least 272 of the patients (80.2%) in the intervention arm were treated in compliance with the approval of bimekizumab.

According to the SPC, the use of adalimumab is not restricted to methotrexate in the case of combination treatment with a csDMARD. However, as part of the concomitant therapy with sulfasalazine and hydroxychloroquine sulphate in the BE OPTIMAL study, the use of drugs that are not approved for this therapeutic indication was also permitted. In the BE OPTIMAL study, 11 of the patients (10.2%) in the adalimumab arm received concomitant sulfasalazine and thus an off-label therapy. Hydroxychloroquine sulphate, on the other hand, was not used in the control arm.

In total, a minimum of 272 and a maximum of 290 patients (80.2% and 85.5% respectively) in the intervention arm and 97 patients (89.8%) in the comparator arm were treated with an

approval-compliant concomitant therapy. This means that a maximum of 17.4% of patients in the subpopulation presented received an unapproved concomitant therapy.

Summary

There are various uncertainties about the subpopulation presented by the company. It is not clear from the information provided by the company whether all patients in the subpopulation had had an inadequate response or had been intolerant to prior csDMARD therapy. In addition, in some of the patients in both study arms, the use of csDMARDs was not in compliance with the approval. For the latter point of criticism, it is ensured that at least 80% of the subpopulation were treated in compliance with the approval. However, even assuming that at least 80% of the subpopulation presented also fulfil the criterion of inadequate response or intolerance, it is overall unclear whether at least 80% of the patients in the analysed subpopulation meet the present research question. The subpopulation presented by the company is thus not used for the benefit assessment.

In both treatment arms, the subpopulation relevant for the benefit assessment comprises only patients who had received either monotherapy or combination therapy with methotrexate and for whom it is ensured that there was an insufficient response or intolerance to the prior csDMARD therapy.

Overall, no suitable data are therefore available to assess the added benefit of bimekizumab in comparison with the ACT in bDMARD-naive patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior DMARD therapy. There is no hint of an added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit[3]

Since the subpopulation presented by the company is unsuitable to assess the added benefit of bimekizumab in comparison with the ACT in bDMARD-naive patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior DMARD therapy, an added benefit is not proven.

[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].

Research question 2: patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior bDMARD therapy

Concurring with the company, no relevant study was identified for research question 2.

Results

No data are available to assess the added benefit of bimekizumab in comparison with the ACT in patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior bDMARD therapy. There is no hint of an added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit

Since the company presented no data to assess the added benefit of bimekizumab in comparison with the ACT in patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior bDMARD therapy, an added benefit is not proven.

Probability and extent of added benefit – summary

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	Adults with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior DMARD[b] therapy[c]	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 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

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**.
b. This refers to csDMARDs.
c. The patient population considered for research question 1 consists of bDMARD-naive patients.

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

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of bimekizumab, alone or in combination with methotrexate, in comparison with the ACT in adult patients with active psoriatic arthritis if response to prior DMARD therapy was inadequate or this therapy was not tolerated.

The research questions shown in Table 4 are derived from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of bimekizumab

Research question	Therapeutic indication	ACT[a]
1	Adults with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior DMARD[b] therapy[c]	A TNF-alpha antagonist (**adalimumab** or certolizumab pegol or etanercept or golimumab or infliximab) or an interleukin inhibitor (ixekizumab or secukinumab or ustekinumab), if applicable in combination with methotrexate
2	Adults with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior therapy with 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

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**.
b. This refers to csDMARDs.
c. The patient population considered for research question 1 consists of bDMARD-naive patients.

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

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

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

The company followed the specification of the ACT for both research questions. For research question 1, the company chose adalimumab from the specified options. For research question 2, the company did not choose a drug from the named options and did not include any studies, either.

The assessment is 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 are used for deriving the added benefit. This concurs with the company's inclusion criteria.

I 3 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

I 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: 17 April 2023)
- bibliographical literature search on bimekizumab (last search on 17 April 2023)
- search in trial registries/trial results databases for studies on bimekizumab (last search on 17 April 2023)
- search on the G-BA website for bimekizumab (last search on 17 April 2023)

To check the completeness of the study pool:

- search in trial registries for studies on bimekizumab (last search on 6 July 2023); for search strategies, see I Appendix A of the full dossier assessment

The company identified the BE OPTIMAL study [3-9] for the direct comparison of bimekizumab versus adalimumab. The company used a subpopulation, which it considered to be a relevant, for the benefit assessment. It is unclear for this subpopulation, however, whether at least 80% of the patients correspond to the present question. The analyses of this study presented by the company are therefore unsuitable for the present benefit assessment (see below).

No additional relevant study was identified from the check of the completeness of the study pool.

Study included by the company

Study design, patient population and interventions

The BE OPTIMAL study is a double-blind RCT, which compared bimekizumab with adalimumab. The duration of treatment with the study medication was 52 weeks. A total of 852 patients were randomized in a ratio of 3:2:1 to treatment with bimekizumab (N = 431), placebo (N = 281) and adalimumab (N = 140). Randomization was stratified by the factors of region and bone erosion [0, ≥ 1]. After Week 16, patients in the placebo arm were switched to treatment with bimekizumab until Week 52. This placebo arm is not relevant for the benefit assessment and is no longer considered hereinafter. Following the 52-week treatment, patients who had not permanently discontinued the study medication had the opportunity to participate in an unblinded extension study [10].

The study population included adult patients who had active psoriatic arthritis, defined according to CASPAR criteria [11], for at least 6 months. Patients had to have ≥ 3 swollen and ≥ 3 tender joints and active plaque psoriasis or a documented history of plaque psoriasis. In addition, the patients had to be bDMARD-naive. Pretreatment with csDMARDs was possible (see below). Only patients with adult-onset psoriatic arthritis were included.

The dosage of bimekizumab in the intervention arm was mostly in compliance with the specifications in the SPC [12]; deviations are described below. The dosage of adalimumab was in compliance with the approval [13]. Under defined conditions (see Table 8 in the full dossier assessment), treatment with csDMARDs, NSAIDs, COX-2 inhibitors, analgesics and oral corticosteroids initiated before study start could be continued during treatment with the study medication. The following drugs were defined as csDMARDs in the study: methotrexate, sulfasalazine, leflunomide, methotrexate sodium, apremilast, ciclosporin, tofacitinib, hydroxychloroquine sulphate, azathioprine. If there was an insufficient treatment response by Week 16, the concomitant therapy could be adjusted. In the study, the adjustment was referred to as rescue therapy, which comprised initiation or dose increase or treatment switch of therapy with csDMARDs, NSAIDs, COX-2 inhibitors, analgesics or oral corticosteroids. After Week 16, biological therapy could also be considered if no improvement had occurred or was expected with the previously mentioned treatment options. However, the initiation of biological therapy led to the permanent discontinuation of the study medication.

Patients who did not participate in the open-label extension study or who discontinued the study medication prematurely were followed up for 20 weeks with regard to side effects. In the total population, 379 of 431 (87.9%) in the bimekizumab arm and 121 of 140 (86.4%) in the adalimumab arm entered the open-label extension study. For the subpopulation with ≥ 1 csDMARD pretreatments analysed by the company, no data on treatment discontinuation or transition to the open-label extension study are available.

The primary outcome of the study was the ACR50 response at Week 16. Patient-relevant outcomes on morbidity, health-related quality of life and side effects were also recorded.

The company presented analyses at Week 24 and Week 52 (final analysis).

For a characterization of the study, see also Table 7 and Table 8 in I Appendix B of the full dossier assessment.

Suitability of the subpopulation presented by the company for research question 1 is unclear

The approval of bimekizumab is restricted to patients who have had an inadequate response or who have been intolerant to one or more DMARDs [12]. Research question 1 comprises pretreated patients who are bDMARD-naive, i.e. who have only received pretreatment with

at least one csDMARD. However, pretreatment with a csDMARD was not an inclusion criterion in the BE OPTIMAL study. For this reason, the company only used the subpopulation with at least one prior csDMARD therapy who, according to the company, had had an inadequate response or who had been intolerant to csDMARD therapy, for the benefit assessment. Prior therapy includes both therapy that was ongoing at the time of study inclusion and previously completed therapy with csDMARDs. The subpopulation presented by the company comprises 339 patients in the bimekizumab arm and 108 patients in the adalimumab arm. The subpopulation is not used for the benefit assessment. This is justified below.

Inadequate response to prior therapy with a csDMARD

The company justified the inadequate response of patients in the subpopulation with the disease burden at baseline (see Table 9 in the full dossier assessment), the duration of the disease, the inclusion of patients at the investigator's discretion, and the fact that, despite prior csDMARD therapy, patients had to have active psoriatic arthritis according to CASPAR criteria with cutaneous and musculoskeletal manifestations for at least 6 months and be suitable for treatment with adalimumab per local approval.

The company did not provide any specific information on its definition of an inadequate response. The European League Against Rheumatism (EULAR) recommends using bDMARDs if there has been no improvement of at least 50% after 3 months of treatment with csDMARDs and the treatment target has not been achieved after 6 months [14]. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) also recommends for patients with peripheral psoriatic arthritis that the response to csDMARD therapy should be checked regularly and, if necessary, therapy should be escalated after 12 to 24 weeks [15].

Table 5 provides information on csDMARD therapy.

Table 5: Information on the csDMARD therapy – RCT, direct comparison: bimekizumab vs. adalimumab (multipage table)

Study	Patients with therapy n (%)	
	Bimekizumab N = 339	Adalimumab N = 108
BE OPTIMAL		
Prior csDMARD therapy[b]		
Number of prior csDMARD therapies		
1	270 (79.6[c])	90 (83.3[c])
≥ 2	69 (20.4[c])	18 (16.7[c])
csDMARD by active substances[d]		
Methotrexate	269 (79.4)	87 (80.6)
Methotrexate sodium	34 (10.0)	4 (3.7)
Sulfasalazine	52 (15.3)	14 (13.0)
Leflunomide	40 (11.8)	12 (11.1)
Apremilast	13 (3.8)	5 (4.6)
Ciclosporin	6 (1.8)	4 (3.7)
Tofacitinib	5 (1.5)	1 (0.9)
Hydroxychloroquine sulphate	3 (0.9)	0 (0)
Azathioprine	0 (0)	1 (0.9)
Therapy at baseline[e]		
csDMARD		
Yes	301 (88.8)	99 (91.7)
Methotrexate	252 (74.3)	82 (75.9)
No	38 (11.2)	9 (8.3)
Concomitant therapy on ≥ 1 days within the treatment phase[f]		
csDMARD	303 (89.4[c])	99 (91.7[c])
Methotrexate	253 (74.6[c])	82 (75.9[c])
csDMARD and no methotrexate[g]	49 (14.5[c])	17 (15.7[c])
No csDMARD and no methotrexate[g]	38 (11.2[c])	9 (8.3[c])
csDMARD by active substances[d]		
Methotrexate	227 (67.0)	78 (72.2)
Methotrexate sodium	28 (8.3)	5 (4.6)
Sulfasalazine	28 (8.3)	11 (10.2)
Leflunomide	26 (7.7)	8 (7.4)
Apremilast	10 (2.9)	2 (1.9)
Ciclosporin	0 (0)	0 (0)
Tofacitinib	0 (0)	0 (0)
Hydroxychloroquine sulphate	3 (0.9)	0 (0)
Azathioprine	0 (0)	0 (0)

Table 5: Information on the csDMARD therapy – RCT, direct comparison: bimekizumab vs. adalimumab (multipage table)

Study	Patients with therapy n (%)	
	Bimekizumab N = 339	Adalimumab N = 108
a. The following active substances were defined as csDMARDs in the BE OPTIMAL study: methotrexate, sulfasalazine, leflunomide, methotrexate sodium, apremilast, ciclosporin, tofacitinib, hydroxychloroquine sulphate, azathioprine.		
b. All therapies that were started before baseline. These could either be continued at baseline or have been terminated before baseline.		
c. Institute's calculation.		
d. It was possible for patients to receive several of the listed csDMARDs. It is not clear from the available data how many patients received several csDMARDs in parallel or, additionally for concomitant therapies, how high the proportion of patients is who switched therapy.		
e. All therapies that were given at baseline.		
f. This also includes therapies that were not given at baseline.		
g. Concomitant therapies that were started before baseline.		
csDMARD: conventional synthetic DMARD; DMARD: disease-modifying antirheumatic drug; n: number of patients with therapy; N: number of analysed patients; RCT: randomized controlled trial		

Patients with only one prior csDMARD therapy that was still administered at baseline

The duration of pretreatment with a csDMARD is important for assessing whether patients with only one prior csDMARD therapy that was continued at baseline had an inadequate response because, as described above, guidelines recommend to escalate therapy after a treatment duration of 12 weeks to 6 months if response is inadequate or the treatment target is not achieved.

In the BE OPTIMAL study, approximately 80% of the presented subpopulation in both study arms had been pretreated with only one csDMARD prior to inclusion in the study. Since the proportion of patients with concomitant csDMARD therapy at baseline was about 90%, it can be assumed that most of them were continuing their only previous therapy at this time. The company did not provide any information on the duration of pretreatment, but a minimum duration of treatment can be inferred for some of these patients based on the inclusion criteria. Parallel administration of methotrexate or leflunomide was only permitted if it had been started at least 12 weeks before baseline and had been given at a stable dose for at least 8 weeks before randomization. Continuing treatment with sulfasalazine was allowed if this treatment had been started at least 8 weeks before baseline and the dosage had been stable for at least 4 weeks before randomization. A total of 74.7% of patients received methotrexate at baseline and thus had at least 12 weeks of pretreatment with a csDMARD, according to the inclusion criteria. There is no information on how many patients were treated with leflunomide or sulfasalazine at baseline.

Based on the guideline recommendations, 12 weeks is the minimum treatment duration after which therapy can be escalated if the response is insufficient. However, it is unclear whether the treatment duration was actually long enough in all patients to determine a lack of response to treatment. It cannot be directly inferred from the duration of the disease, which was a median of 3.7 years in the bimekizumab arm and 3.2 years in the adalimumab arm (see Table 9 in I Appendix B of the full dossier assessment), that all patients received a longer csDMARD therapy in compliance with the guidelines, to which response was inadequate. Likewise, the available values on disease burden at baseline, such as the patient-reported outcomes of Patient Assessment of Arthritis Pain (PtAAP), Health Assessment Questionnaire-Disability Index (HAQ-DI) and Psoriatic Arthritis Quality of Life (PsAQOL) listed by the company, do not reflect the period over which the therapy existing at baseline had already been administered before the start of the study. The same applies to the company's argument that the inclusion of patients in the study was at the discretion of the investigators, as their decision about suitability for participation in the study was based only on existing symptoms and not additionally on inadequate response to prior therapy. This meant that DMARD-naive patients could also be included. Overall, it is unclear whether all patients who continued their only previous csDMARD therapy during the course of the BE OPTIMAL study had an inadequate response to this therapy, as it cannot be ruled out that some patients had not been treated with a csDMARD for long enough before enrolment to assume an inadequate response.

Patients with prior csDMARD therapy but without treatment at baseline

10.5% of all patients in the presented subpopulation had already discontinued a previous csDMARD therapy before baseline. In this case, the reasons for discontinuation (primary lack of response, secondary lack of response, intolerance, partial response, other) had to be recorded in the eCRF. However, these data were not provided by the company. It therefore remains uncertain whether and to what extent there were reasons other than an inadequate response or intolerance for the discontinuation of treatment.

Suitability for treatment with adalimumab

In order to check whether the inclusion criterion of suitability for treatment with adalimumab per local approval ensures that at least 80% of the patients in the subpopulation presented by the company had had an inadequate response or had been intolerant to prior csDMARD therapy, the local approvals in the countries where the BE OPTIMAL study was conducted were considered. According to the European approval, adalimumab is indicated in patients with an inadequate response to previous basic therapy, so that the indication corresponds to that of bimekizumab [16]. However, not in all countries where the BE OPTIMAL study was conducted, does the local approval necessarily include patients with an inadequate response to prior csDMARD therapy. Whereas the therapeutic indication of adalimumab in Japan, Canada and Australia is comparable to that in Europe [17-19], in the United States,

pretreatment with a csDMARD is not a prerequisite for treatment with adalimumab [20]. No information is available on the therapeutic indication in Russia.

Information on the number of patients included in the BE OPTIMAL study in the individual countries is only available for the total population. According to this, at least 75.5% of patients in the total population had an inadequate response to previous csDMARD therapy at the time of study inclusion. However, it is unclear how high the proportion of patients is in the subpopulation presented.

Thus, the inclusion criterion of suitability for treatment with adalimumab per local approval is also not suitable to determine whether at least 80% of the patients included in the company's subpopulation had had an inadequate response or had been intolerant to prior csDMARD therapy.

Summary

Based on the described uncertainties regarding patients with only one prior csDMARD therapy that was still administered at baseline, csDMARD-pretreated patients without treatment at baseline, and the aspect of suitability for treatment with adalimumab, it is not sufficiently ensured that at least 80% of the patients in the subpopulation presented by the company meet the criterion of insufficient response or intolerance.

Use of csDMARDs was partly not in compliance with the approval

According to the SPC, bimekizumab is approved as monotherapy or in combination with methotrexate [12]. In the BE OPTIMAL study, 252 of the patients (74.3%) in the bimekizumab arm received methotrexate (including methotrexate sodium) at baseline, 49 (14.5%) received a csDMARD other than methotrexate, and 38 (11.2%) received no csDMARD at all (see Table 5). Based on this information, it can initially be assumed that treatment with bimekizumab was initiated at the start of the study in up to 85.5% of the patients in compliance with the approval. However, it was possible to adjust the csDMARD therapy during the course of the study as so-called rescue therapy (see above) and, in principle, to administer several csDMARDs in parallel, both at baseline and in the course of the study. The available information on concomitant treatment neither clearly indicates how many patients received more than one csDMARD in parallel, nor how many patients switched their concomitant csDMARD treatment during the course of the study. Thus, it cannot be ruled out that some of the patients who received concomitant treatment with methotrexate at the start of the study also received another csDMARD not covered by the approval. Based on the information on baseline and concomitant therapy in Table 5, however, the overall proportion of patients who switched to another csDMARD during the course of the study or who received another csDMARD in addition to methotrexate was not higher than 5.3%. This means that at least 272

of the patients (80.2%) in the intervention arm were treated in compliance with the approval of bimekizumab.

According to the SPC, the use of adalimumab is not restricted to methotrexate in the case of combination treatment with a csDMARD [13]. However, as part of the concomitant therapy with sulfasalazine and hydroxychloroquine sulphate in the BE OPTIMAL study, the use of drugs that are not approved for this therapeutic indication was also permitted [21,22]. The use of sulfasalazine is nevertheless recommended across guidelines [14,15,23], resulting in a discrepancy between guideline recommendations and approval. In the BE OPTIMAL study, 11 of the patients (10.2%) in the adalimumab arm received concomitant sulfasalazine and thus an off-label therapy; the other 97 patients (89.8%) were treated in compliance with the approval. Hydroxychloroquine sulphate, on the other hand, was not used in the control arm (see Table 5).

In total, a minimum of 272 and a maximum of 290 patients (80.2% and 85.5% respectively) in the intervention arm and 97 patients (89.8%) in the comparator arm were treated with an approval-compliant concomitant therapy. This means that a maximum of 17.4% of patients in the subpopulation presented received an unapproved concomitant therapy.

Summary

There are various uncertainties about the subpopulation presented by the company. It is not clear from the information provided by the company whether all patients in the subpopulation had had an inadequate response or had been intolerant to prior csDMARD therapy. In addition, in some of the patients in both study arms, the use of csDMARDs was not in compliance with the approval. For the latter point of criticism, it is ensured that at least 80% of the subpopulation were treated in compliance with the approval. However, even assuming that at least 80% of the subpopulation presented also fulfil the criterion of inadequate response or intolerance, it is overall unclear whether at least 80% of the patients in the analysed subpopulation meet the present research question. The subpopulation presented by the company is thus not used for the benefit assessment.

In both treatment arms, the subpopulation relevant for research question 1 of the benefit assessment comprises only patients who had received either monotherapy or combination therapy with methotrexate and for whom it is ensured that there was an insufficient response or intolerance to the prior csDMARD therapy.

Further points of criticism

Different bimekizumab dosage for coexistent moderate to severe plaque psoriasis

In the BE OPTIMAL study, bimekizumab was administered subcutaneously at a dose of 160 mg every 4 weeks. This is in compliance with the approved dosage for patients with psoriatic

arthritis. For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, a different dosage is recommended, i.e. 320 mg subcutaneously at Week 0, 4, 8, 12, 16 and every 8 weeks thereafter. After 16 weeks, a switch to 160 mg every 4 weeks can be considered if a sufficient clinical response in joints cannot be maintained [12].

In general, the severity of plaque psoriasis has not been clearly defined. For example, according to the 2004 *Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis*, the European Medicines Agency (EMA) considers a Psoriasis Area and Severity Index (PASI) > 10 or Body Surface Area (BSA) involvement > 10% to be a suitable operationalization for moderate to severe plaque psoriasis [24]. The 2011 European consensus defines moderate to severe plaque psoriasis as "(BSA > 10 or PASI > 10) and Dermatology Life Quality Index (DLQI) > 10" [25]. Alongside the 2011 definition, the 2020 EuroGuiDerm guideline also offers several definitions without defining specific thresholds [26]. 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 [27].

In the dossier, the company defined moderate to severe plaque psoriasis as PASI > 10, but only presented the proportion of patients with PASI ≥ 10. The DLQI was not recorded in the BE OPTIMAL study. The presence of the "upgrade criteria" listed in the S3 guideline cannot be assessed on the basis of the information presented either. Thus, severity can be assessed only using the instruments for recording the cutaneous manifestation. At the start of the BE OPTIMAL study, 11.5% of patients in the bimekizumab arm had PASI ≥ 10, and 16.5% had BSA > 10%. It is therefore assumed that more than 10% of patients did not receive the recommended bimekizumab dosage despite the uncertainty regarding the PASI threshold.

The greatest discrepancy between the dosages existed during the first 16 weeks of treatment, for which twice the amount of active substance is recommended for patients with coexistent moderate to severe plaque psoriasis. After 16 weeks, the dosages approximated each other, and from this point onwards it was also possible to switch to the dosage of 160 mg every 4 weeks used in the study, which is in compliance with the SPC. Since the analyses at Week 52 are primarily relevant for the benefit assessment due to the longer observation period, it is assumed that the existing deviation in the later course of the study has no important influence on the results.

Outcomes

Analyses based on a limited study population

For the following outcomes, the company only included patients in its responder analyses who had the following disease activity at the start of the study:

- Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index: only patients with SPARCC > 0 at baseline
- Leeds Enthesitis Index (LEI): only patients with LEI > 0 at baseline
- Leeds Dactylitis Index (LDI): only patients with LDI > 0 at baseline
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI): only patients with a value of ≥ 4 at baseline
- PASI: only patients with psoriasis on ≥ 3% of BSA at baseline
- modified Nail Psoriasis Severity Index (mNAPSI): only patients with mNAPSI > 0 at baseline
- 12-item Psoriatic Arthritis Impact of Disease (PsAID-12): only patients with a value of ≥ 3 at baseline
- Health Assessment Questionnaire-Disability Index (HAQ-DI): only patients with a value of ≥ 0.45 at baseline
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F): only patients with a value of ≤ 44.2 at baseline

The approach of the company is 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. Thus, the total study population and the relevant subpopulation are at risk for these outcomes. Due to the operationalization chosen by the company, it may not be possible to derive conclusions for the total target population. It is therefore necessary to include all patients of the subpopulation in the analysis of these outcomes. Such analyses are generally possible for the outcomes that were recorded for all patients in the study. However, in accordance with the study protocol, PASI and mNAPSI were only recorded during the course of the study in patients who had a certain level of disease activity at baseline (see above). These were 49.0% of patients in the subpopulation presented by the company for the PASI, and 55.3% for the mNAPSI. Unless at least 70% of the subpopulation are included in the analysis, the responder analyses for these instruments are not suitable for the benefit assessment.

Serious adverse events (SAEs)

For the presentation of the results on common SAEs, the company used a cut-off value for the intervention arm that differs from that of the dossier template [28]. As described in the dossier template, in addition to events that occurred in at least 5% of patients in one study arm, events that occurred in at least 10 patients and in at least 1% of patients in one study arm should also be shown in the presentation of SAEs by organ systems and individual events.

Discontinuation due to adverse events (AEs)

In the dossier, the company presented the outcome "discontinuation due to AEs" operationalized as AEs that led to study discontinuation. However, there is no information on AEs that led to treatment discontinuation, although according to the study protocol, both AEs that led to treatment discontinuation and AEs that led to study discontinuation were to be recorded.

I 3.2 Results on added benefit

No suitable data are available to assess the added benefit of bimekizumab in comparison with the ACT in bDMARD-naive patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior DMARD therapy. There is no hint of an added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

I 3.3 Probability and extent of added benefit

Since the subpopulation presented by the company is unsuitable to assess the added benefit of bimekizumab in comparison with the ACT in bDMARD-naive patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior DMARD therapy, an added benefit is not proven.

I 4 Research question 2: patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior bDMARD therapy

I 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: 17 April 2023)
- bibliographical literature search on bimekizumab (last search on 17 April 2023)
- search in trial registries/trial results databases for studies on bimekizumab (last search on 17 April 2023)
- search on the G-BA website for bimekizumab (last search on 17 April 2023)

To check the completeness of the study pool:

- search in trial registries for studies on bimekizumab (last search on 6 July 2023); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check identified no relevant study.

I 4.2 Results on added benefit

No data are available to assess the added benefit of bimekizumab in comparison with the ACT in patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior bDMARD therapy. There is no hint of an added benefit of bimekizumab in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

Since the company presented no data to assess the added benefit of bimekizumab in comparison with the ACT in patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to prior bDMARD therapy, an added benefit is not proven.

I 5 Probability and extent of added benefit – summary

Table 6 summarizes the result of the assessment of added benefit of bimekizumab in comparison with the ACT.

Table 6: 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 DMARD[b] therapy[c]	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 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

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**.
b. This refers to csDMARDs.
c. The patient population considered for research question 1 consists of bDMARD-naive patients.

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

For research question 1, the assessment described above deviates from that by the company, which derived an indication of minor added benefit for bDMARD-naive patients. For research question 2, for patients who have had an inadequate response or who have been intolerant to prior therapy with bDMARDs, the company also did not claim an added benefit.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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