IQWiG Reports – Commission No. A20-112

Guselkumab (psoriatic arthritis) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Guselkumab (Psoriasis-Arthritis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 24 February 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Guselkumab (psoriatic arthritis) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
1 December 2020

Internal Commission No.
A20-112

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Keywords: Guselkumab, Arthritis – Psoriatic, Benefit Assessment, NCT02207231, NCT02207244, NCT03796858, NCT03162796, NCT01077362

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
bDMARD	biologic disease-modifying antirheumatic drug
BSA	body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
csDMARD	conventional synthetic disease-modifying antirheumatic drugs
DMARD	disease-modifying antirheumatic drug
DLQI	Dermatology Life Quality Index
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
hf-PGA	Physician Global Assessment of Hands and/or Feet
IGA	Investigator Global Assessment
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MTX	methotrexate
NAPSI	Nail Psoriasis Severity Index
NSAID	nonsteroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PSSD	Psoriasis Symptoms and Signs Diary
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SHI	statutory health insurance
SF-36	Short Form 36 Health Survey
SPC	Summary of Product Characteristics
sPGA	static Physician Global Assessment
ss-IGA	Scalp-specific Investigator Global Assessment
TNF	tumour necrosis factor

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug guselkumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 December 2020.

Research question

The aim of the present report is the assessment of the added benefit of guselkumab, alone or in combination with methotrexate (MTX), in comparison with the appropriate comparator therapy (ACT) in adult patients with active psoriatic arthritis who have had an inadequate response to a prior disease-modifying antirheumatic drug (DMARD) therapy.

The ACT differs depending on the pretreatment of the patients. The resulting research questions are shown in Table 2.

Table 2: Research questions of the benefit assessment of guselkumab

Research question	Subindication	ACT[a]
1	Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy[b]	A TNF-alpha antagonist **(adalimumab** or certolizumab pegol or etanercept or golimumab or infliximab) or an IL-17 inhibitor (ixekizumab), possibly in combination with methotrexate
2	Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior biologic disease-modifying antirheumatic drug (bDMARD) therapy	Switch to another biologic disease-modifying antirheumatic (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab or **ustekinumab**), possibly in combination with methotrexate

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. The patient population considered for research question 1 consists of bDMARD-naive patients.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; IL17: interleukin-17; TNF: tumour necrosis factor

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

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 a prior DMARD therapy

Study pool and study characteristics

The company submitted the studies VOYAGE 1 and VOYAGE 2 for its benefit assessment. These studies were already included in the first assessment of guselkumab in patients with plaque psoriasis (IQWiG assessment A17-60).

The studies VOYAGE 1 and VOYAGE 2 are randomized, double-blind studies conducted worldwide. Both studies investigated guselkumab in comparison with placebo and adalimumab in adults with plaque psoriasis. Both studies included patients with moderate to severe plaque psoriasis who were candidates for either systemic therapy or phototherapy and who were either naive to systemic treatment or had already received systemic treatment. The presence of psoriatic arthritis was not a prerequisite for inclusion in the studies. Patients who had psoriatic arthritis in addition to plaque psoriasis could be included in the studies, however.

Only those patients who had psoriatic arthritis in addition to plaque psoriasis are relevant for the present benefit assessment. The company therefore presented analyses of subpopulations with patient-reported symptomatic psoriatic arthritis from both studies. The approach of the company is comprehensible. The defined subpopulations are generally eligible for the assessment of the added benefit of guselkumab in psoriatic arthritis. Guselkumab is approved for the treatment of active psoriatic arthritis. However, there is no characterization of the disease in the dossier, apart from the duration of the disease. In particular, there is a lack of information on whether the patients had active psoriatic arthritis, for example based on the Classification Criteria for Psoriatic Arthritis (CASPAR).

Results

The results presented by the company on patient-relevant symptom outcomes refer exclusively to the therapeutic indication of plaque psoriasis. These cannot be adequately interpreted without information on specific outcomes for the therapeutic indication of psoriatic arthritis.

To assess the added benefit of guselkumab in patients with psoriatic arthritis, at least a lesser benefit for specific psoriatic arthritis outcomes must be excluded. This requires results on outcomes for psoriatic arthritis-specific symptoms (supplemented by assessments of health-related quality of life). However, these are not available in the company's dossier and were also not recorded in the studies VOYAGE 1 and VOYAGE 2.

In summary, the company did not provide any suitable data in its dossier for the assessment of the added benefit of guselkumab in psoriatic arthritis for patients with psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior DMARD therapy. This resulted in no hint of an added benefit of guselkumab in comparison with the ACT; an added benefit is therefore not proven.

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

No RCTs of direct comparison were identified for the assessment of the added benefit of guselkumab versus the comparator therapy ustekinumab in patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior bDMARD therapy. The company presented an adjusted indirect comparison using the common comparator placebo with 2 studies on the guselkumab side and 1 study on the ustekinumab side. These were the studies COSMOS and DISCOVER 1 (each with guselkumab versus placebo) on the one hand, and PSUMMIT 2 (ustekinumab versus placebo) on the other. As both on the guselkumab side and on the ustekinumab side, only RCTs versus placebo are available in the relevant therapeutic indication, in agreement with the company, placebo is the only possible common comparator for an adjusted indirect comparison.

Study pool and study characteristics

Each of the studies was conducted in patients with active psoriatic arthritis who had had an inadequate response or who had been intolerant to pretreatment with DMARDs. These DMARDs were bDMARDs in the COSMOS study, and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in the studies DISCOVER 1 and PSUMMIT 2. However, the assessment of the added benefit of guselkumab is to be conducted in patients who have had an inadequate response or who have been intolerant to bDMARDs. The company therefore identified subpopulations in the studies that corresponded to the research question.

Study COSMOS (guselkumab versus placebo)

The COSMOS study is a double-blind RCT on the comparison of guselkumab with placebo. It included patients with active psoriatic arthritis who had had an inadequate response or who had been intolerant to pretreatment with up to 2 tumour necrosis factor alpha (TNF) inhibitors. The patients were randomized to guselkumab or placebo in a 2:1 ratio (189 versus 96 patients). The treatment duration was 48 weeks in total, with all patients in the placebo arm being treated with guselkumab from week 24. The study recorded outcomes on all-cause mortality, arthritis-related morbidity, plaque psoriasis-related morbidity, health-related quality of life and side effects.

For its assessment, the company excluded patients receiving concomitant treatment with csDMARDs other than MTX. This approach is appropriate. In the relevant subpopulation, there were 173 patients in the guselkumab arm and 86 patients in the placebo arm.

Study DISCOVER 1 (guselkumab versus placebo)

The DISCOVER 1 study is a double-blind RCT on the comparison of guselkumab with placebo. It included patients with active psoriatic arthritis who had had an inadequate response or who had been intolerant to pretreatment with csDMARDs. In addition, prior therapy with up to 2 TNF inhibitors was possible, but had to be completed at least 4 weeks before the start of the study. Patients were randomized in a 1:1:1 ratio to guselkumab every 4 weeks, guselkumab

every 8 weeks or placebo (128 versus 127 versus 126 patients). The 4-week arm is not relevant for the assessment. The total treatment duration was 52 weeks, with all patients in the placebo arm receiving guselkumab after 24 weeks.

The study recorded outcomes on all-cause mortality, arthritis-related morbidity, plaque psoriasis-related morbidity, health-related quality of life and side effects.

The company considered a subpopulation of patients who had been pretreated with a TNF inhibitor and who had discontinued their prior therapy due to inadequate response or intolerance, and who did not receive any csDMARDs other than MTX in addition to ustekinumab or placebo. The relevant subpopulation of the company represents a sufficient approximation to the target population. It comprises 22 patients in the guselkumab arm and 19 patients in the placebo arm.

Study PSUMMIT 2 (ustekinumab versus placebo)

The PSUMMIT 2 study is a double-blind RCT on the comparison of ustekinumab with placebo. It included patients with active psoriatic arthritis who had had an inadequate response or who had been intolerant to pretreatment with csDMARDs and/or nonsteroidal anti-inflammatory drugs (NSAIDs), but possibly also to prior therapy with TNF inhibitors. Patients were randomized in a 1:1:1 ratio to ustekinumab 45 mg, ustekinumab 90 mg or placebo (103 versus 105 versus 104 patients). The 90 mg arm is not relevant for the assessment and is therefore not considered further. The total treatment duration was 52 weeks, with all patients in the placebo arm receiving ustekinumab after 24 weeks.

The study recorded outcomes on all-cause mortality, arthritis-related morbidity, plaque psoriasis-related morbidity, health-related quality of life and side effects.

The company considered a subpopulation from which it excluded patients who had not been previously treated with a TNF inhibitor or who received a csDMARD other than MTX in addition to ustekinumab or placebo. The relevant subpopulation of the study comprises 26 patients in the ustekinumab arm and 24 patients in the placebo arm.

Therapy adjustment in the studies at week 16 (early escape)

All 3 studies offered the possibility of receiving an adjustment to the existing therapy (early escape) from week 16 under certain conditions. In the studies COSMOS and PSUMMIT 2, early escape in the placebo arms consisted of a switch to the respective intervention. In the DISCOVER 1 study, the study treatments remained unchanged in early escape, and only the concomitant therapy was adjusted.

Similarity of the studies for the indirect comparison

The studies COSMOS, DISCOVER 1 and PSUMMIT 2 show no major differences in terms of the patients included, so that these are considered sufficiently similar. However, due to the different early escape strategies at week 16, sufficient similarity between the common

comparators no longer existed after this time point. However, the indirect comparison conducted by the company is not suitable for the benefit assessment also for other reasons (see following paragraph). The homogeneity assumption of the 2 included studies on guselkumab was therefore not checked.

Risk of bias

The results of the adjusted indirect comparison presented by the company are not usable for the benefit assessment; this is justified below.

Results from adjusted indirect comparisons have a low certainty of results per se. Only adjusted indirect comparisons of high methodological quality and with a sufficient number of studies with low risk of bias, in which a valid check of the assumption of homogeneity and consistency has been carried out, can be considered as having a moderate certainty of results. If there is only one study with a high risk of bias for one side of the included direct comparison for an adjusted indirect comparison using an adequate common comparator, no hint of an added benefit or greater/lesser harm is regularly derived.

The risk of bias across outcomes was rated as high both for the results of the COSMOS study and for those of the PSUMMIT 2 study. This was due to the high proportion of patients in the placebo arm who switched to treatment with guselkumab or ustekinumab due to non-response at week 16 (early escape). For example, at the relevant time of analysis (week 24), 48% of patients in the placebo arm in the COSMOS study had switched to guselkumab, and 25% of patients in the placebo arm in the PSUMMIT 2 study had switched to ustekinumab. All patient-relevant outcomes are affected by the risk of bias.

Since there is therefore only one study with moderate certainty of results on the side of the direct comparison of ustekinumab with the common comparator placebo (study PSUMMIT 2) in the adjusted indirect comparison, the uncertainty in the available data is overall too high to be able to derive valid conclusions on the added benefit or greater/lesser harm of guselkumab in comparison with the ACT. Irrespective of the limitations described, the indirect comparison did not show a statistically significant difference between guselkumab and ustekinumab for any of the outcomes included by the company.

Results

The indirect comparison conducted by the company is not usable. Hence, the company's dossier did not contain any relevant data on the added benefit of guselkumab in comparison with the ACT. This resulted in no hint of an added benefit of guselkumab in comparison with the ACT; an added benefit is therefore not proven.

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

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

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

Table 3: Guselkumab – probability and extent of added benefit

Subindication	ACT[a]	Probability and extent of added benefit
Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy[b]	A TNF-alpha antagonist **(adalimumab** or certolizumab pegol or etanercept or golimumab or infliximab) or an IL-17 inhibitor (ixekizumab), possibly in combination with methotrexate	Added benefit not proven
Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior biologic disease-modifying antirheumatic drug (bDMARD) therapy	Switch to another biologic disease-modifying antirheumatic (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab or **ustekinumab**), possibly in combination with methotrexate	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. The patient population considered for research question 1 consists of bDMARD-naive patients.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; IL17: interleukin-17; TNF: tumour necrosis factor

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

[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].

2.2 Research question

The aim of the present report is the assessment of the added benefit of guselkumab, alone or in combination with MTX, in comparison with the ACT in adult patients with active psoriatic arthritis who have had an inadequate response to a prior DMARD therapy.

The ACT differs depending on the pretreatment of the patients. The resulting research questions are shown in Table 4.

Table 4: Research questions of the benefit assessment of guselkumab

Research question	Subindication	ACT[a]
1	Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy[b]	A TNF-alpha antagonist **(adalimumab** or certolizumab pegol or etanercept or golimumab or infliximab) or an IL-17 inhibitor (ixekizumab), possibly in combination with methotrexate
2	Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior biologic disease-modifying antirheumatic drug (bDMARD) therapy	Switch to another biologic disease-modifying antirheumatic (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab or **ustekinumab**), possibly in combination with methotrexate

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. The patient population considered for research question 1 consists of bDMARD-naive patients.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; IL17: interleukin-17; TNF: tumour necrosis factor

In the present assessment, the following terms 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 a prior DMARD therapy
- Research question 2: patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a 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 chose ustekinumab.

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

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

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on guselkumab (status: 16 November 2020)
- bibliographical literature search on guselkumab (last search on 23 October 2020)
- search in trial registries/trial results databases for studies on guselkumab (last search on 2 November 2020)
- search on the G-BA website for guselkumab (last search on 22 October 2020)

To check the completeness of the study pool:

- search in trial registries for studies on guselkumab (last search on 4 December 2020)

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

2.3.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: guselkumab 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])
CNTO1959PSO3001 (VOYAGE 1[d])	Yes[e]	Yes	No	No[f]	Yes [3,4]	Yes [5-14]
CNTO1959PSO3002 (VOYAGE 2[d])	Yes[e]	Yes	No	No[f]	Yes [15,16]	Yes [5-14,17]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website.
d. In the following tables, the study is referred to with this abbreviated form.
e. The studies were submitted by the company for the approval of guselkumab in the therapeutic indication of plaque psoriasis.
f. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial; vs.: versus

2.3.1.2 Study characteristics

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
VOYAGE 1	RCT, double-blind	Treatment-naive or pretreated[b] adults (≥ 18 years) with plaque psoriasis (IGA ≥ 3, PASI ≥ 12 and BSA ≥ 10) for at least 6 months before study start, with or without psoriatic arthritis	Guselkumab (N = 329) placebo[c] (N = 174) adalimumab (N = 334) Relevant subpopulation thereof: guselkumab (n = 25) adalimumab (n = 24)	Screening: about 4 weeks Treatment: ▪ blinded treatment phase: until week 48 ▪ open-label extension phase[d]: until week 160 Observation: until week 160	101 centres in Australia, Canada, Germany, Hungary, Poland, Russia, South Korea, Spain, Taiwan, USA 12/2014–6/2020	Primary: PASI 90, IGA score of 0 or 1 Secondary: all-cause mortality, symptoms, health-related quality of life, AEs
VOYAGE 2	RCT, double-blind	Treatment-naive or pretreated[b] adults (≥ 18 years) with plaque psoriasis (IGA ≥ 3, PASI ≥ 12 and BSA ≥ 10) for at least 6 months before study start, with or without psoriatic arthritis	Guselkumab (N = 496) placebo[c] (N = 248) adalimumab (N = 248) Relevant subpopulation thereof: guselkumab (n = 41) adalimumab (n = 21)	Screening: about 4 weeks Treatment: ▪ blinded treatment phase: until week 24 ▪ randomized treatment discontinuation and resumed treatment[e]: week 28 until week 76 ▪ open-label extension phase[d]: until week 160 Observation: until week 160	115 centres in Australia, Canada, Czech Republic, Germany, Poland, Russia, South Korea, Spain, USA 11/2014–7/2020	Primary: PASI 90, IGA score of 0 or 1 Secondary: all-cause mortality, symptoms, health-related quality of life, AEs

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

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

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Systemic treatment or phototherapy.
c. The arm is not relevant for the assessment and is no longer presented in the following tables.
d. In the open-label extension phase, patients of all study arms were treated with guselkumab. Due to lack of comparison, this study phase is not relevant for the assessment and is not shown in the following tables.
e. From week 28, patients of all study arms who had not achieved PASI 90 received (continued) treatment with guselkumab. Patients in the guselkumab arm who had achieved PASI 90 were re-randomized in week 28 to continued treatment with guselkumab or treatment discontinuation with resumed guselkumab treatment (on 50% loss of the achieved PASI improvement). Patients in the adalimumab and placebo arm with PASI 90 response discontinued treatment and received subsequent guselkumab treatment on 50% loss of the achieved PASI improvement. Due to lack of comparison, this study phase is not relevant for the assessment and is not shown in the following tables.

AE: adverse event; BSA: body surface area; IGA: Investigator Global Assessment; n: relevant subpopulation; N: number of randomized patients; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: guselkumab vs. adalimumab (multipage table)

Study	Intervention	Comparison
VOYAGE 1	Guselkumab 100 mg SC in week 0, 4 and 12, then every 8 weeks until week 44 + placebo for guselkumab in week 16 + placebo for adalimumab 2x 0.8 mL SC in week 0, followed by 1x 0.8 mL in week 1, 3 and 5, then every 2 weeks until week 47	Adalimumab 2x 40 mg per 0.8 mL SC in week 0, and 1x 40 mg in week 1, 3 and 5, then every 2 weeks until week 47 + placebo for guselkumab in week 0, 4, 12, 16 and 20, then every 8 weeks until week 44
VOYAGE 2	Guselkumab 100 mg SC in week 0, 4, 12 and 20 + placebo for guselkumab in week 16 + placebo for adalimumab 2x 0.8 mL SC in week 0, followed by 1x 0.8 mL in week 1, 3 and 5, then every 2 weeks until week 23	Adalimumab 2x 40 mg per 0.8 mL SC in week 0, and 1x 40 mg in week 1, 3 and 5, then every 2 weeks until week 23 + placebo for guselkumab in week 0, 4, 12, 16 and 20
	Prior and concomitant treatment (VOYAGE 1, VOYAGE 2) ***Pretreatment*** Permitted pretreatment ▪ phototherapy ▪ systemic treatment for psoriasis Non-permitted pretreatment ▪ adalimumab ▪ biologic TNFα therapy within 3 months or 5 half-lives before first administration of the study medication ▪ direct-acting drugs against IL-12, IL-17 or IL-23 within 6 months before first administration of the study medication ***Concomitant treatment*** Permitted concomitant treatment ▪ shampoos containing tar or salicylic acid[a] ▪ topical moisturizer[a] ▪ NSAID at a stable dosage ▪ chloroquine ▪ corticosteroids for conditions other than psoriasis for ≤ 2 weeks ▪ inhaled corticosteroids or corticosteroids that are used in the eyes, ears or nose, or other corticosteroids used on the mucosa	

Table 7: Characteristics of the interventions – RCT, direct comparison: guselkumab vs. adalimumab (multipage table)

Study	Intervention	Comparison
	Non-permitted concomitant treatment: ▪ topical treatments that may influence the psoriasis (such as corticosteroids, tar, anthralin, calcipotriol, tazarotene, methoxsalen, pimecrolimus, tacrolimus, traditional Taiwanese, Korean or Chinese substances) ▪ phototherapy ▪ systemic treatment for psoriasis ▪ systemic herbal agents or traditional Taiwanese, Korean or Chinese substances ▪ other biologic or systemic drugs that may influence the psoriasis ▪ Sulfasalazine, gold IM ▪ antimalaria drugs only after week 48 ▪ no live vaccines during the study or within 3 months after the last dose of the study medication no BCG vaccination during the study or within 12 months after the last dose of the study medication	
a. Not allowed on the day of the study visit. BCG: bacille Calmette-Guérin; IL: interleukin; IM: intramuscular; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; SC: subcutaneous; TNF: tumour necrosis factor; vs.: versus		

The company submitted the studies VOYAGE 1 and VOYAGE 2 for its benefit assessment. These studies were already included in the first assessment of guselkumab in patients with plaque psoriasis (IQWiG assessment A17-60) [10].

The studies VOYAGE 1 and VOYAGE 2 are randomized, double-blind studies conducted worldwide. Both studies investigated guselkumab in comparison with placebo and adalimumab in adults with plaque psoriasis. Both studies included patients with moderate to severe plaque psoriasis (involved body surface area [BSA] ≥ 10, Psoriasis Area and Severity Index [PASI] ≥ 12 and static Physician Global Assessment [sPGA] ≥ 3) who were candidates for either systemic therapy or phototherapy, and who either were naive to systemic therapy or have previously received systemic therapy. The presence of psoriatic arthritis was not a prerequisite for inclusion in the studies. Patients who had psoriatic arthritis in addition to plaque psoriasis could be included in the studies, however (see below).

A total of 837 patients (VOYAGE 1) and 992 patients (VOYAGE 2) were randomly allocated in a ratio of 2:1:2 (VOYAGE 1) and 2:1:1 (VOYAGE 2) to the study arms with guselkumab, placebo or adalimumab. The placebo arms are not relevant for the present assessment and are therefore not considered further. Randomization was stratified by study centres in both studies.

Treatment in both studies, both in the guselkumab and in the adalimumab arms, was conducted according to the regimens described in Table 7 and was largely in compliance with the respective Summaries of Product Characteristics (SPCs) [18,19].

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

The design of both studies comprised a 4-week screening phase, followed by a blinded treatment phase of 24 weeks (VOYAGE 2) or 48 weeks (VOYAGE 1). Further details on the study design can be found in the first benefit assessment of guselkumab [10].

Subpopulation relevant for the benefit assessment

Only those patients who had psoriatic arthritis in addition to plaque psoriasis are relevant for the present benefit assessment. The company therefore presented analyses of subpopulations with patient-reported symptomatic psoriatic arthritis from both studies. As a further criterion, the subpopulations only include patients who have been pretreated with at least one csDMARD, but not with bDMARDs. According to the company, all patients in this subpopulation had received MTX as prior therapy. In order to reflect the criterion of inadequate response or intolerance to previous DMARD treatment, patients who had discontinued MTX therapy for other than medical reasons were not included in the relevant subpopulations.

The approach of the company is comprehensible. The defined subpopulations are generally eligible for the assessment of the added benefit of guselkumab in psoriatic arthritis. They include 49 patients in the VOYAGE 1 study and 62 in the VOYAGE 2 study. Guselkumab is approved for the treatment of active psoriatic arthritis. However, there is no characterization of the disease in the dossier, apart from the duration of the disease. In particular, there is a lack of information on whether the patients had active psoriatic arthritis at baseline, for example based on the CASPAR criteria (see Table 8). As the results of the available studies do not allow the derivation of an added benefit in the present therapeutic indication of psoriatic arthritis due to the missing recording of specific outcomes of psoriatic arthritis, this has no further consequences for the benefit assessment.

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

Table 8: Characteristics of the study populations – RCT, direct comparison: guselkumab vs. adalimumab (research question 1) (multipage table)

Study Characteristic Category	VOYAGE 1		VOYAGE 2	
	Guselkumab	Adalimumab	Guselkumab	Adalimumab
	N[a] = 25	N[a] = 24	N[a] = 41	N[a] = 21
Age category [years], n (%)				
< 45	7 (28)	11 (46)	19 (46)	11 (52)
≥ 45 to < 65	15 (60)	13 (54)	22 (54)	10 (48)
≥ 65	3 (12)	0 (0)	0 (0)	0 (0)
Sex [F/M], %	32/68	33/67	29/71	38/62
Family origin, n (%)				
White	21 (84)	22 (92)	40 (98)	18 (86)
Other	4 (16)	2 (8)	1 (2)	3 (14)
Geographical region, n (%)				
North America	2 (8)	4 (17)	1 (2)	1 (5)
Other	23 (92)	20 (83)	40 (98)	20 (95)
Duration of psoriatic arthritis [years], n (%)				
< 15	10 (40)	9 (38)	17 (41)	12 (57)
≥ 15	15 (60)	15 (63)	24 (59)	9 (43)
Subtype of psoriatic arthritis, n (%)	ND	ND	ND	ND
Swollen joint count, n (%)	ND	ND	ND	ND
Tender joint count at baseline, n (%)	ND	ND	ND	ND
Patients with dactylitis, n (%)	ND	ND	ND	ND
Patients with enthesitis, n (%)	ND	ND	ND	ND
PASI score, n (%)				
< 20	12 (48)	6 (25)	16 (39)	9 (43)
≥ 20	13 (52)	18 (75)	25 (61)	12 (57.1)
Pretreatment with non-biologic systemic therapy, n (%)	25 (100)	24 (100)	41 (100)	21 (100)
Number of previous non-biologic systemic therapies	ND	ND	ND	ND
Concomitant therapy with oral corticosteroids at baseline, n (%)	ND	ND	ND	ND
Concomitant therapy with NSAIDs at baseline, n (%)	ND	ND	ND	ND
Treatment discontinuation, n (%)	2 (8)	1 (4)	0 (0)	0 (0)
Study discontinuation, n (%)	ND	ND	ND	ND

a. Number of randomized patients.

F: female; M: male; n: number of patients in the category, N: number of randomized patients; ND: no data; NSAID: nonsteroidal anti-inflammatory drug; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; vs.: versus

For the relevant subpopulations of the studies VOYAGE 1 and VOYAGE 2, there were no important differences between the study arms. The studies as a whole are also comparable.

Slightly more than half of the patients were between 45 and 65 years old; only individual patients represented the > 65 years age group. With about 2 thirds, men were in the majority. About 90% of the patients were white. Regarding origin, it was only stated that individual patients came from North America, the origin of the others was not broken down.

There was almost no information in the company's dossier on the patient characteristics of psoriatic arthritis, the disease relevant for the benefit assessment. Information on the manifestation, disease severity, number and damage of the joints involved was lacking. There is only information on the duration of psoriatic arthritis. Slightly more than half of all patients in both studies had already had the condition for ≥ 15 years.

All patients were pretreated with at least one non-biologic systemic therapy. The company did not provide any information on the type of these therapies, except that all patients had been pretreated with MTX.

Risk of bias across outcomes (study level)

The risk of bias of the studies VOYAGE 1 and VOYAGE 2 was already assessed in A17-60, the first assessment of guselkumab, and was rated as low [10]. Although a different subpopulation is considered in the current dossier than in assessment A17-60, it is assumed that this does not result in a change in the risk of bias across outcomes. However, the company did not report results for the relevant subpopulations for all patient-relevant outcomes of the first assessment in its dossier. For example, it did not present results on patient-reported symptoms. The company did not justify its approach. Therefore, selective reporting cannot be ruled out, which would possibly result in a high risk of bias. This is irrelevant for the present assessment, as there are no results from the studies presented regarding outcomes that allow the derivation of an added benefit in the therapeutic indication of psoriatic arthritis (see Section 2.3.2.1).

The company assessed the risk of bias of both studies as low.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - remission (PASI 100)
  - patient-reported symptoms (Psoriasis Symptoms and Signs Diary [PSSD])
  - no psoriasis symptoms on the scalp (Scalp-specific Investigator Global Assessment [ss-IGA] 0)

- no psoriasis symptoms on the hands and feet (Physician Global Assessment of Hands and/or Feet [hf-PGA] 0)
- no psoriasis symptoms on the nails (Nail Psoriasis Severity Index [NAPSI] 0)
- arthritis-related symptoms

- Health-related quality of life
  - Dermatology Life Quality Index (DLQI) 0 or 1
  - Short Form 36 Health Survey (SF-36)
  - arthritis-related health-related quality of life
- Side effects
  - adverse events (AEs)
  - serious AEs (SAEs)
  - AEs that led to treatment discontinuation
  - further specific AEs, if any

Table 9 shows for which outcomes data were available in the studies included.

Table 9: Matrix of outcomes – RCT, direct comparison: guselkumab vs. adalimumab

Study	Outcomes											
	All-cause mortality	**Remission (PASI 100)**	**Patient-reported symptoms (PSSD)**	**No psoriasis symptoms on the scalp (ss-IGA 0)**	**No psoriasis symptoms on hands and feet (hf-PGA 0)**	**No psoriasis symptoms on the nails (NAPSI 0)**	**Arthritis-related symptoms**	**Health-related quality of life (DLQI 0 or 1)**	**Health-related quality of life (SF-36)**	**Arthritis-related health-related quality of life**	**SAEs**	**Discontinuation due to AEs**
VOYAGE 1	Yes	Yes	No[a]	No[a]	No[a]	Yes	No[b]	Yes	No[b]	No[b]	Yes	Yes
VOYAGE 2	Yes	Yes	No[a]	No[a]	No[a]	Yes	No[b]	Yes	Yes	No[b]	Yes	Yes

a. No data available for the relevant subpopulation.
b. Outcome not recorded.

AE: adverse event; DLQI: Dermatology Life Quality Index; hf-PGA: Physician Global Assessment of Hands and/or Feet; NAPSI: Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index; PSSD: Psoriasis Symptoms and Signs Diary; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form 36 Health Survey; ss-IGA: Scalp-specific Investigator Global Assessment; vs.: versus

Relevance of the available results for the therapeutic indication of psoriatic arthritis

The results presented by the company on patient-relevant symptom outcomes refer exclusively to the therapeutic indication of plaque psoriasis. These cannot be adequately interpreted without information on specific outcomes for the therapeutic indication of psoriatic arthritis. This is justified below.

Results for the subpopulations of the studies VOYAGE 1 and VOYAGE 2 and their meta-analytical summary are presented in Appendix A of the full dossier assessment. Analogous to the first assessment, a fixed-effect model is assumed to be suitable for a meta-analytical summary of the studies. The results for week 48 of the VOYAGE 2 study are not presented because there are no suitable data in the present benefit assessment to assess the added benefit of guselkumab in psoriatic arthritis (see below). Specific AEs are not considered, as no balancing of benefit and harm is possible anyway due to the lack of specific benefit outcomes.

For the outcome category of symptoms, the company presented results on patient-relevant outcomes only from the therapeutic indication of plaque psoriasis, such as the PASI 100. The PASI score is used by the physician to estimate the extent and spread of the symptoms of psoriatic plaque redness, thickness and scaling. Results on outcomes that reflect psoriatic arthritis-related symptoms, including patient-reported outcomes, are completely missing. These would include, for example, information on disease activity, pain, tender and swollen joint count, dactylitis or enthesitis, and physical functional status. Results on psoriatic arthritis-specific outcomes were presented in previous benefit assessments and used to assess the added benefit in the therapeutic indication of psoriatic arthritis [20,21].

For the outcome category of health-related quality of life, results are available for the DLQI, an instrument to assess the impact of a dermatological disease such as plaque psoriasis on health-related quality of life. In addition, results for the SF-36, a generic questionnaire for patients' self-assessment of health-related quality of life, are available for the VOYAGE 2 study. In the absence of psoriatic arthritis-specific symptom outcomes, results on generic quality of life only are not interpretable.

The outcomes included by the company were already assessed for the therapeutic indication of plaque psoriasis in dossier assessment A17-60. The relevance of these outcomes is also given for patients with psoriatic arthritis and concomitant plaque psoriasis. To assess the added benefit of guselkumab in patients with psoriatic arthritis, at least a lesser benefit for specific psoriatic arthritis outcomes must be excluded. This requires results on patient-relevant outcomes for psoriatic arthritis-specific symptoms (supplemented by assessments of health-related quality of life), however. However, these are not available in the company's dossier and were also not recorded in the studies VOYAGE 1 and VOYAGE 2. Thus, a balancing of benefit and harm of guselkumab for this disease is not possible on the basis of the available data.

In summary, the company did not provide any suitable data in its dossier for the assessment of the added benefit of guselkumab in psoriatic arthritis for patients with psoriatic arthritis who

have had an inadequate response or who have been intolerant to a prior DMARD therapy. This resulted in no hint of an added benefit of guselkumab in comparison with the ACT; an added benefit is therefore not proven.

Transferability of the study results to the German health care context

According to the company, the results for the subpopulation of patients with psoriatic arthritis and concomitant moderate to severe plaque psoriasis are transferable to the German health care context. It derived this from the following facts:

Firstly, according to a routine data analysis of the German statutory health insurance (SHI), 84% of all patients with psoriatic arthritis who have not responded to a csDMARD also have plaque psoriasis, of which 10% to 35% with moderate to severe manifestations [22-25]. According to the company, this also applies to the relevant subpopulations of the studies VOYAGE 1 and VOYAGE 2, which have a high degree of congruence with the target population. Furthermore, the studies were conducted in Germany, about 90% of the patients were of white family origin and the dosing regimen implemented for adalimumab was adequate and in compliance with the approval for the subpopulation with active psoriatic arthritis and moderate to severe plaque psoriasis. Besides, contacts with dermatologists had significant relevance for comorbid patients with moderate to severe plaque psoriasis and concomitant psoriatic arthritis, the company added. In 50% of these patients, the first prescription of biologics was made by a dermatologist.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.3.3 Probability and extent of added benefit

The company did not present any data suitable for deriving an added benefit in bDMARD-naive patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior DMARD therapy. An added benefit of guselkumab in comparison with the ACT is therefore not proven.

This deviates from the assessment of the company, which derived an indication of a minor added benefit for this patient group.

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

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on guselkumab (status: 16 November 2020)
- bibliographical literature search on guselkumab (last search on 23 October 2020)
- search in trial registries/trial results databases for studies on guselkumab (last search on 2 November 2020)
- search on the G-BA website for guselkumab (last search on 2 November 2020)
- study list on the ACT (status: 16 November 2020)
- bibliographical literature search for the ACT (last search on 17 September 2020)
- search in trial registries/trial results databases for the ACT (last search on 2 November 2020)
- search on the G-BA website for the ACT (last search on 2 November 2020)

To check the completeness of the study pool:

- search in trial registries for studies on guselkumab (last search on 4 December 2020)
- search in trial registries for studies on the ACT (last search on 7 December 2020)

Concurring with the company, no relevant RCT was identified for the present research question. The company therefore aimed for an adjusted indirect comparison based on RCTs, and identified 3 studies for this purpose. The check identified the additional relevant PSA 2001 study [26,27], which the company had not included in its study pool. See Section 2.4.1.1.

2.4.1.1 Studies included

For the assessment of the added benefit of guselkumab, the company presented an adjusted indirect comparison using the common comparator placebo with 2 studies on the guselkumab side and one study on the ustekinumab side. As both on the guselkumab side and on the ustekinumab side, only RCTs versus placebo are available in the relevant therapeutic indication, in agreement with the company, placebo is the only possible common comparator for an adjusted indirect comparison.

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

Table 10: Study pool – RCT, indirect comparison: guselkumab vs. ustekinumab

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
Studies with guselkumab						
CNTO1959PSA3003 (COSMOS[c])	No	Yes	No	No[d]	Yes [28,29]	No
CNTO1959PSA3001 (DISCOVER 1[c])	Yes	Yes	No	No[d]	Yes [30,31]	Yes [32]
Study with ustekinumab						
CNTO1275PSA3002 (PSUMMIT 2[c])	Yes	Yes	No	No[d]	Yes [33,34]	Yes [35-38]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.
d. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

CSR: clinical study report; RCT: randomized controlled trial; vs.: versus

In its study list, the company also mentioned the PSA 2001 study comparing guselkumab versus placebo, which was also identified by the check of the company's search. It excluded this study from its study pool because only 10 patients in the guselkumab arm and 4 patients in the placebo arm met the inclusion and exclusion criteria of the research question. However, this is not a sufficient justification for non-inclusion, as the study is relevant for the indirect comparison. In addition, some of the relevant subpopulations of the studies included by the company also only had low double-digit patient numbers (see Table 11 of the present benefit assessment).

Due to the small number of patients, it is nevertheless assumed that the non-consideration of the PSA 2001 study does not have a significant impact on the results of the indirect comparison. The benefit assessment can therefore be carried out with the study pool of the company.

Figure 1 shows a schematic representation of the indirect comparison.

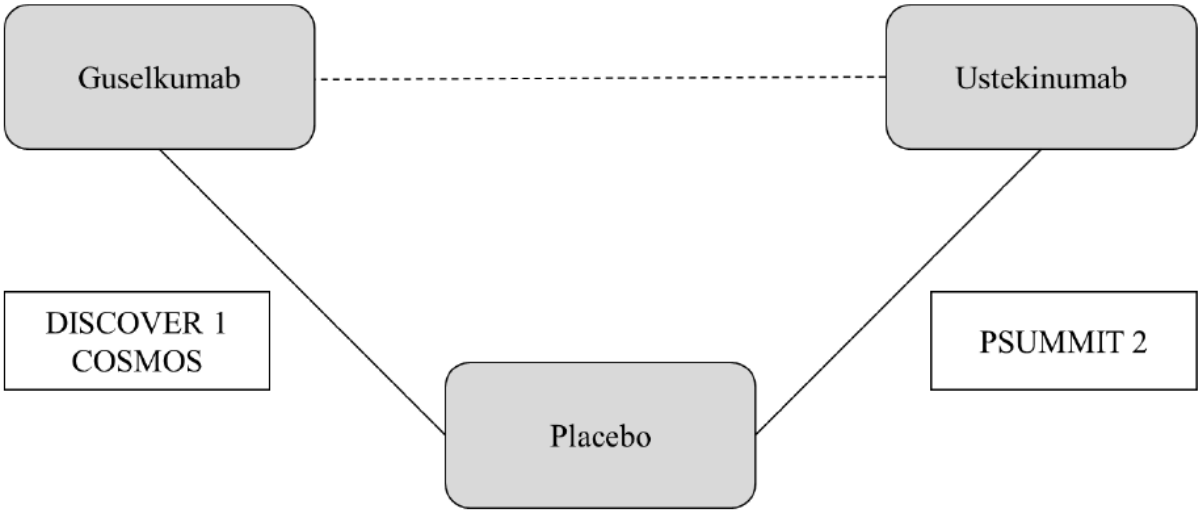

Figure 1: Study pool for the indirect comparison between guselkumab and the comparator therapy ustekinumab

2.4.1.2 Study characteristics

Table 11 and Table 12 describe the studies used for the benefit assessment.

Table 11: Characteristics of the studies included – indirect comparison: guselkumab vs. ustekinumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Studies with guselkumab						
COSMOS	RCT, double-blind, parallel	Adults with active psoriatic arthritis[b] who have had an inadequate response or who have been intolerant to 1 or 2 prior therapies with TNF inhibitors	Guselkumab (N = 189) placebo (N = 96) Relevant subpopulation thereof[c]: guselkumab (n = 173) placebo (n = 86)	Screening: up to 6 weeks Treatment: 48 weeks (placebo arm: switch to guselkumab after 24 weeks) Follow-up: 8 weeks (safety)	84 centres in: Belgium, Bulgaria, France, Germany, Hungary, Israel, Italy, Poland, Portugal, Russia, Spain, Ukraine, United Kingdom 3/2019–ongoing Data cut-off at week 24: 3 August 2020	Primary: ACR 20 at week 24 Secondary: morbidity, health-related quality of life, AEs
DISCOVER 1	RCT, double-blind, parallel	Adult patients with active psoriatic arthritis[b] who have had an inadequate response or who have been intolerant to a previous conventional standard therapy of psoriatic arthritis and who may also have been pretreated with TNF inhibitors	Guselkumab every 4 weeks (N = 128)[d] Guselkumab every 8 weeks (N = 127) placebo (N = 126) subpopulation thereof analysed by the company[e]: guselkumab every 8 weeks (n = 22) placebo (n = 19)	Screening: up to 6 weeks Treatment: 52 weeks (placebo arm: switch to guselkumab after 24 weeks) Follow-up: 8–12 weeks (safety)	86 centres in Australia, Canada, Czech Republic, Germany, Hungary, Malaysia, Poland, Russia, South Korea, Spain, Taiwan, Ukraine, USA 8/2017–11/2019 Data cut-off at week 24: 14 March 2019	Primary: ACR 20 at week 24 Secondary: morbidity, health-related quality of life, AEs

Table 11: Characteristics of the studies included – indirect comparison: guselkumab vs. ustekinumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Study with ustekinumab						
PSUMMIT 2	RCT, double-blind, parallel	Adults with active psoriatic arthritis[f] who have had an inadequate response or who have been intolerant to a previous conventional standard therapy and possibly biologic therapy with TNF inhibitors	Ustekinumab 45 mg (N = 103) Ustekinumab 90 mg (N = 105)[d] placebo (N = 104) Relevant subpopulation thereof[g]: ustekinumab 45 mg (n = 26) placebo (n = 24)	Screening: up to 6 weeks Treatment: 52 weeks (placebo arm: switch to ustekinumab after 24 weeks) Follow-up: 8 weeks (safety)	71 centres in: Austria, Canada, France, Germany, Hungary, Poland, Russia, Sweden, United Kingdom, USA 2/2010–11/2012 Data cut-off at week 24: 21 March 2012	Primary: ACR 20 at week 24 Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively contain data on relevant available outcomes from the information provided by the company in Module 4 of the dossier.
b. Diagnosis according to CASPAR, with ≥ 3 tender and ≥ 3 swollen joints, both at screening and at baseline, and at least one of the following psoriatic arthritis manifestations: distal interphalangeal joint involvement, polyarticular arthritis with absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis; in the DISCOVER 1 study, an additional serum concentration of ≥ 0.3 mg/dL C-reactive protein at screening.
c. Patients who received concomitant therapy with a csDMARD other than methotrexate were excluded.
d. The arm is not relevant for the assessment and is no longer presented in the following tables.
e. Patients who were not pretreated with a TNF inhibitor were excluded, as were patients for whom a reason for discontinuation other than inadequate response or intolerance was given or who received concomitant therapy with a csDMARD other than methotrexate.
f. Diagnosis of active psoriatic arthritis at screening defined by ≥ 5 tender and ≥ 5 swollen joints both at screening and at baseline and a serum concentration of ≥ 0.3 mg/dL C-reactive protein at screening (criterion changed from ≥ 0.6 mg/dL after Amendment 3) and at least one of the following psoriatic arthritis manifestations: distal interphalangeal joint involvement, polyarticular arthritis with the absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis.
g. Patients who have not been pretreated with TNF inhibitors or have received concomitant therapy with a csDMARD other than methotrexate are excluded.

ACR: American College of Rheumatology; AE: adverse event; CASPAR: Classification Criteria for Psoriatic Arthritis; csDMARD: conventional synthetic DMARD; DMARD: disease-modifying antirheumatic drug; n: subpopulation; N: number of randomized patients; RCT: randomized controlled trial; TNF: tumour necrosis factor; vs.: versus

Table 12: Characteristics of the intervention – RCT, indirect comparison: guselkumab vs. ustekinumab (multipage table)

Study	Intervention	Comparison
Studies with guselkumab		
COSMOS	Guselkumab 100 mg SC at week 0, 4, then every 8 weeks	Placebo SC
	In case of inadequate response[a] at week 16 (early escape):	
	option to initiate or increase the dose of one of the permitted concomitant medications	switch to guselkumab at week 16; then 100 mg at weeks 16 and 20, then every 8 weeks; additional option to initiate or increase dose of one of the permitted concomitant medications
	Pretreatment Required: ▪ 1-2 TNF inhibitors with inadequate response or intolerance to therapy ▪ non-biologic DMARDs ▫ if taken at baseline: stable dosage ▫ Patients not using these medications at baseline: discontinuation of therapy ≥ 4 weeks (for MTX, sulfasalazine, or hydroxychloroquine), ≥ 12 weeks (leflunomide); only 1 csDMARD allowed at baseline Allowed: ▪ low-dose oral corticosteroids or NSAIDs: ▫ if taken at baseline: stable dosage, or ▫ discontinuation of therapy ≥ 2 weeks Not allowed: ▪ ≥ 2 TNF inhibitors or use of TNF inhibitors 4–8 weeks prior to first administration of the study medication: ▪ biologics other than TNF inhibitors ▪ JAK inhibitors ▪ immunosuppressants ≤ 4 weeks before first administration of the study medication ▪ other csDMARDs except MTX, sulfasalazine, hydroxychloroquine, leflunomide, or systemic immunosuppressants within 4 weeks before first administration of the study medication ▪ apremilast ≤ 4 weeks before first administration of the study medication ▪ light therapy and other systemic medications that could affect the evaluation of psoriasis ≤ 4 weeks before first administration of the study medication ▪ topical drugs for the treatment of psoriasis ≤ 2 weeks before first administration of the study medication ▪ corticosteroids and lithium ≤ 4 weeks before first administration of the study medication ▪ investigational antibody, biologic or other therapy ≤ 90 days or 5 half-lives (whichever is longer) before first administration of the study medication	
	Concomitant treatment Allowed: 1 of the following concomitant therapies, continuation of stable dosage before start of study: ▪ NSAIDs or other analgesics, low-dose oral corticosteroids (≤ 10 mg prednisone per day or equivalent) ▪ csDMARDs (MTX ≤ 25 mg/week, sulfasalazine ≤ 3 g/day, hydroxychloroquine ≤ 400 mg/day or leflunomide ≤ 20 mg/day) Not allowed: no data	

Table 12: Characteristics of the intervention – RCT, indirect comparison: guselkumab vs. ustekinumab (multipage table)

Study	Intervention	Comparison
DISCOVER 1	Guselkumab 100 mg SC, every 8 weeks[b]	Placebo SC
	In case of inadequate response[a] at week 16: option to initiate or increase dose of one of the permitted concomitant medications (early escape)	
	Pretreatment: Required: ▪ ≤ 2 TNF inhibitors: with inadequate response or intolerance to therapy ▪ inadequate response or intolerance to standard therapy of psoriatic arthritis including non-biologic DMARDs (≥ 3 months), apremilast (≥ 4 months) and/or NSAID therapy (≥ 4 weeks) before first administration of the study medication Allowed: ▪ non-biologic DMARDs: ▫ if taken at baseline: start of therapy ≥ 3 months and stable dose for ≥ 4 weeks, only 1 csDMARD allowed at baseline, or ▫ patients not using these medications at baseline: discontinuation of therapy ≥ 4 weeks (for MTX, sulfasalazine, or hydroxychloroquine), ≥ 12 weeks (leflunomide) in case of inadequate response or intolerance; ▪ low-dose oral corticosteroids: ▫ if taken at baseline: stable dose for ≥ 2 weeks (≤ 10 mg/day prednisone or equivalent), or ▫ patients not using these medications at baseline: discontinuation of therapy ≥ 2 weeks before first use of the study medication ▪ NSAIDs and other analgesics: ▫ if taken at baseline: stable dose for < 2 weeks, or ▫ patients not using these medications at baseline: discontinuation of therapy ≥ 2 weeks before first use of the study medication Not allowed: ▪ > 2 TNF inhibitors or use of TNF inhibitors 4–8 weeks prior to first administration of the study medication ▪ bDMARDs other than TNF inhibitors or investigational treatment ▪ JAK inhibitors ▪ systemic immunosuppressants ≤ 4 weeks before first use of the study medication ▪ other non-biologic DMARDs except MTX ≤ 4 weeks before first administration of the study medication ▪ apremilast ≤ 4 weeks before first use of the study medication ▪ corticosteroids and lithium ≤ 4 weeks before first administration of the study medication ▪ light therapy and other systemic medications that could affect the evaluation of psoriasis ≤ 4 weeks before first administration of the study medication ▪ topical drugs for the treatment of psoriasis ≤ 2 weeks before first administration of the study medication	

Table 12: Characteristics of the intervention – RCT, indirect comparison: guselkumab vs. ustekinumab (multipage table)

Study	Intervention	Comparison
	Concomitant treatment Allowed: 1 of the following concomitant therapies, continuation of stable dosage before start of study: ▪ NSAIDs or other analgesics, low-dose oral corticosteroids (≤ 10 mg/day prednisone or equivalent) ▪ non-biologic DMARDs (MTX ≤ 25 mg/week, sulfasalazine ≤ 3 g/day, hydroxychloroquine ≤ 400 mg/day or leflunomide ≤ 20 mg/day) ▪ when taking MTX: ≥ 5 mg folate or folic acid weekly Not allowed: see non-permitted pretreatment; additionally: no live vaccines	
Study with ustekinumab		
PSUMMIT 2	Ustekinumab 45 mg SC at week 0 and 4, then every 12 weeks	Placebo SC
	In case of inadequate response[a] at week 16 (early escape):	
	dose increase to 90 mg in week 16, then every 12 weeks until week 40	switch to ustekinumab 45 mg in week 16, 20, 28, and then every 12 weeks until week 40
	Pretreatment Required: ▪ standard therapy of psoriatic arthritis including non-biologic DMARDs (≥ 3 months), apremilast (≥ 4 months) and/or NSAID (≥ 4 weeks) before first administration of the study medication, with inadequate response or intolerance ▪ ≥ 1 TNF inhibitor: Allowed: ▪ MTX at baseline: start of treatment ≥ 3 months and stable dose of ≤ 25 mg/week for ≥ 4 weeks before study start and no serious toxic side effects ▪ NSAIDs or other analgesics for psoriatic arthritis ▫ if taken at baseline: stable dosage for ≥ 2 weeks before taking the first study medication, or ▫ discontinuation ≤ 2 weeks before taking the first study medication ▪ oral corticosteroids ▫ if taken at baseline: stable dosage (equivalent to prednisone 10 mg/day) for ≥ 2 weeks before taking the first study medication, or ▫ discontinuation ≤ 2 weeks before taking the first study medication	

Table 12: Characteristics of the intervention – RCT, indirect comparison: guselkumab vs. ustekinumab (multipage table)

Study	Intervention	Comparison
	Not allowed: ▪ IL-12 or IL-23 inhibitors, e.g. ustekinumab ▪ investigational drugs ≤ 4 weeks before study start or 5 half-lives (whichever is longer) before study start ▪ infliximab, golimumab or certolizumab pegol < 12 weeks before first administration of the study medication; etanercept or adalimumab ≤ 8 weeks before first administration of the study medication ▪ alpha 4 integrin antagonists, efalizumab or drugs that modulate B- or T-cells ≤ 12 months before screening ▪ alefacept ≤ 3 months before administration of the study medication ▪ abatacept ▪ other csDMARDs except MTX ≤ 4 weeks before first administration of the study medication ▪ anakinra ≤ 4 weeks before first administration of the study medication ▪ leflunomide ≤ 4 weeks before administration of the first study medication (regardless of discontinuation process) or within 4–12 weeks before administration of the study medication without completing a discontinuation process ▪ any systemic medication or treatment that may affect the psoriasis or PASI evaluation ≤ 4 weeks before first administration of the study medication ▪ topical treatment that could affect the psoriasis or PASI evaluation ≤ 2 weeks before first administration of the study medication ▪ any systemic immunosuppressants ≤ 4 weeks before administration of the study medication ▪ corticosteroids and lithium ≤ 4 weeks before first administration of the study medication ▪ live vaccines ≤ 3 months before first administration of the study medication, during the study and 12 months after the last administration of the study medication **Concomitant treatment** Allowed: 1 of the following concomitant therapies, continuation of stable dosage before start of study: ▪ NSAIDs or other analgesics, oral corticosteroids ▪ MTX Not allowed: ▪ non-biologic DMARDs other than MTX
a. < 5% improvement in swollen and tender joint count. b. According to the approval, guselkumab is given at week 0, 4 and 8, then every 8 weeks. bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; DMARD: disease-modifying antirheumatic drug; IA: intraarticular; IL: interleukin; IM: intramuscular; IV: intravenous; JAK: Janus kinase; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; SC: subcutaneous; TNF: tumour necrosis factor; vs.: versus		

Each of the studies was conducted in patients with active psoriatic arthritis who had had an inadequate response or who had been intolerant to pretreatment with DMARDs. These DMARDs were bDMARDs in the COSMOS study, and csDMARDs in the studies DISCOVER 1 and PSUMMIT 2. However, the assessment of the added benefit of guselkumab is to be conducted in patients who have had an inadequate response or who have been intolerant

to bDMARDs. The company therefore identified subpopulations in the studies that corresponded to the research question. The studies and the relevant subpopulations are described in more detail below:

COSMOS (guselkumab versus placebo)

The COSMOS study is a double-blind RCT on the comparison of guselkumab with placebo. It included patients with active psoriatic arthritis who had had an inadequate response or who had been intolerant to pretreatment with up to 2 TNF inhibitors (bDMARDs). The patients were randomized to guselkumab or placebo in a 2:1 ratio (189 versus 96 patients). The dosage and administration of guselkumab was in compliance with the approval [18]. The treatment duration was 48 weeks in total, with all patients in the placebo arm being treated with guselkumab from week 24. Hence, only the period until the treatment switch is relevant for the benefit assessment. The company presented a data cut-off that covers the first 24 weeks of treatment. The study recorded outcomes on all-cause mortality, arthritis-related morbidity, plaque psoriasis-related morbidity, health-related quality of life and side effects.

During treatment with guselkumab or placebo, concomitant treatment with csDMARDs was possible. However, the approval of guselkumab only allows concomitant treatment with MTX. The company therefore excluded patients who received csDMARDs other than MTX. This approach is appropriate. In the relevant subpopulation, there were 173 patients in the guselkumab arm and 86 patients in the placebo arm.

DISCOVER 1 (guselkumab versus placebo)

The DISCOVER 1 study is a double-blind RCT on the comparison of guselkumab with placebo. It included patients with active psoriatic arthritis who had had an inadequate response or who had been intolerant to pretreatment with csDMARDs. In addition, prior therapy with up to 2 TNF inhibitors was possible, but had to be completed at least 4 weeks before the start of the study. Patients were randomized in a 1:1:1 ratio to guselkumab every 4 weeks, guselkumab every 8 weeks or placebo (128 versus 127 versus 126 patients). The 4-week arm is not relevant for the assessment and is therefore not considered further. The dosage and administration of guselkumab was in compliance with the approval [18].

The total treatment duration was 52 weeks, with all patients in the placebo arm receiving guselkumab after 24 weeks. Hence, only the period until the treatment switch is relevant for the benefit assessment. The company presented a data cut-off that covers the first 24 weeks of treatment. The study recorded outcomes on all-cause mortality, arthritis-related morbidity, plaque psoriasis-related morbidity, health-related quality of life and side effects.

Since the present research question refers to patients with an inadequate response or intolerance to bDMARDs, but not csDMARDs, the company considered a subpopulation of the study. This subpopulation includes patients who were pretreated with a TNF inhibitor and who discontinued their prior therapy due to inadequate response or intolerance. The company excluded patients for whom other reasons for discontinuation were documented. In addition,

patients who received a csDMARD other than MTX in addition to ustekinumab or placebo were excluded. This approach is appropriate. Since bDMARDs are usually administered only after treatment with csDMARDs has been unsuccessful, it is assumed that the most recent pretreatment was with TNF inhibitors. The relevant subpopulation of the company thus represents a sufficient approximation to the target population. It comprises 22 patients in the guselkumab arm and 19 patients in the placebo arm.

PSUMMIT 2 (ustekinumab versus placebo)

The PSUMMIT 2 study is a double-blind RCT on the comparison of ustekinumab with placebo. It included patients with active psoriatic arthritis who had had an inadequate response or who had been intolerant to pretreatment with csDMARDs and/or NSAIDs, but possibly also to prior therapy with TNF inhibitors. In addition, prior therapy with up to 2 TNF inhibitors was possible, but had to be completed at least 8 weeks before the start of the study. Patients were randomized in a 1:1:1 ratio to ustekinumab 45 mg, ustekinumab 90 mg or placebo (103 versus 105 versus 104 patients). The 90 mg arm is not relevant for the assessment and is therefore not considered further. The dosage and administration of ustekinumab was in compliance with the approval [39].

The total treatment duration was 52 weeks, with all patients in the placebo arm receiving ustekinumab after 24 weeks. Hence, only the period until the treatment switch is relevant for the benefit assessment. The company presented a data cut-off that covers the first 24 weeks of treatment. The study recorded outcomes on all-cause mortality, arthritis-related morbidity, plaque psoriasis-related morbidity, health-related quality of life and side effects.

Since the present research question refers to patients with an inadequate response or intolerance to bDMARDs, but not csDMARDs, the company excluded patients who had not been previously treated with a TNF inhibitor from its analysis. In addition, patients who received a csDMARD other than MTX in addition to ustekinumab or placebo were excluded. This approach is appropriate. The relevant subpopulation of the study comprises 26 patients in the ustekinumab arm and 24 patients in the placebo arm.

Therapy adjustment in the studies at week 16 (early escape)

All 3 studies offered the possibility of receiving an adjustment to the existing therapy (early escape) from week 16. The prerequisite for this early escape in each case was that the swollen and tender joint count did not decrease by at least 5% within this period. Table 13 shows that the early escape measures varied between the studies.

Table 13: Early escape strategies in the included studies

	COSMOS	**DISCOVER 1**	**PSUMMIT 2**
Relevant subpopulation	Guselkumab (N = 173) vs. placebo (N = 86)	Guselkumab (N = 22) vs. placebo (N = 19)	Ustekinumab (N = 26) vs. placebo (N = 24)
Therapy adjustment (early escape) from week 16 in case of non-response	Placebo arm: switch from placebo to guselkumab Intervention arm: continuation of guselkumab In both arms, it is also possible to start or increase the dose of concomitant therapy	Start or dose increase of concomitant therapy	Placebo arm: switch from placebo to 45 mg ustekinumab Intervention arm: dose increase to 90 mg ustekinumab
Number of patients with early escape, n (%)	Guselkumab: 36 (20.8) Placebo: 41 (47.7)	Guselkumab: 2 (9.1) Placebo: 6 (31.6)	Ustekinumab: 3 (11.5) Placebo: 6 (25.0)
Handling of early escape patients by the company in the analysis	Consideration as non-responders	Consideration as non-responders	Updating of the last available value before week 16
N: number of included patients in the relevant subpopulation			

In the studies COSMOS and PSUMMIT 2, early escape in the placebo arms consisted of a switch to the respective intervention. In the COSMOS study, this affected about 48% of patients in the placebo arm, and 25% in the PSUMMIT 2 study. Besides, in the PSUMMIT 2 study, almost 12% of the patients in the intervention arm switched to a dose of ustekinumab that is only approved for a body weight of > 100 kg. In the DISCOVER 1 study, the study treatments remained unchanged in early escape, and only the concomitant therapy was adjusted.

The company's approach regarding treatment switch, particularly in the PSUMMIT 2 study, affects the risk of bias of the study results and consequently on the usability of the data for the indirect comparison (see Section 2.4.1.5 on the risk of bias across outcomes).

Patient characteristics

Table 14 shows the characteristics of the patients in the studies included.

Table 14: Characteristics of the study populations – RCT, indirect comparison: guselkumab vs. ustekinumab (research question 2) (multipage table)

Study Characteristics Category	Studies with guselkumab				Study with ustekinumab	
	COSMOS		DISCOVER 1		PSUMMIT 2	
	Guselkumab	Placebo	Guselkumab	Placebo	Ustekinumab	Placebo
	N[a] = 173	N[a] = 86	N[a] = 22	N[a] = 19	N[a] = 26	N[a] = 24
Age category [years], n (%)						
< 45	63 (36)	28 (33)	7 (32)	4 (21)	9 (35)	4 (17)
≥ 45 to < 65	91 (53)	51 (59)	14 (64)	12 (63)	16 (62)	18 (75)
≥ 65	19 (11)	7 (8)	1 (5)	3 (16)	1 (4)	2 (8)
Sex [F/M], %	57/43	45/55	50/50	68/32	65/35	46/54
Family origin, n (%)						
White	ND	ND	18 (82)	15 (79)	26 (100)	24 (100)
Other	ND	ND	4 (18)	4 (21)	0 (0)	0 (0)
Geographical region, n (%)						
Poland	ND	ND	6 (27)	3 (16)	ND	ND
Russia	ND	ND	5 (23)	2 (11)	ND	ND
Ukraine	ND	ND	1 (5)	4 (21)	ND	ND
Western Europe and North America	ND	ND	5 (23)	7 (37)	ND	ND
Other country	ND	ND	5 (23)	3 (16)	ND	ND
Europe	ND	ND	ND	ND	13 (50)	8 (33)
North America	ND	ND	ND	ND	13 (50)	16 (67)
Duration of psoriatic arthritis [years], n (%)						
< 1	5 (3)	1 (1)	0 (0)	0 (0)	1 (4)	1 (4)
≥ 1 to < 3	30 (17)	14 (16)	7 (32)	0 (0)	6 (23)	3 (13)
≥ 3	138 (80)	71 (83)	15 (68)	19 (100)	19 (73)	20 (83)

Table 14: Characteristics of the study populations – RCT, indirect comparison: guselkumab vs. ustekinumab (research question 2) (multipage table)

Study Characteristics Category	Studies with guselkumab				Study with ustekinumab	
	COSMOS		DISCOVER 1		PSUMMIT 2	
	Guselkumab	Placebo	Guselkumab	Placebo	Ustekinumab	Placebo
	N[a] = 173	N[a] = 86	N[a] = 22	N[a] = 19	N[a] = 26	N[a] = 24
Subtype of psoriatic arthritis, n (%)						
Distal interphalangeal joint involvement	15 (9)	6 (7)	2 (9)	0 (0)	4 (15)	2 (8)
Polyarticular arthritis with the absence of rheumatoid nodules	55 (32)	26 (30)	1 (5)	0 (0)	11 (42)	14 (58)
Arthritis mutilans	2 (1)	1 (1)	11 (50)	8 (42)	0 (0)	0 (0)
Asymmetric peripheral arthritis	60 (35)	31 (36)	5 (23)	6 (32)	6 (23)	5 (21)
Spondylitis with peripheral arthritis	40 (23)	22 (26)	3 (14)	5 (26)	5 (19)	3 (13)
Unknown	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Swollen joint count at baseline, n (%)						
< 10	106 (61)	58 (67)	14 (64)	13 (68)	8 (31)	13 (54)
10 to ≤ 15	39 (23)	19 (22)	3 (14)	3 (16)	3 (12)	6 (25)
> 15	28 (16)	9 (10)	5 (23)	3 (16)	15 (58)	5 (21)
Tender joint count at baseline, n (%)						
< 10	25 (14)	19 (22)	6 (27)	2 (11)	1 (4)	4 (17)
≥ 10 to ≤ 15	43 (25)	25 (29)	6 (27)	9 (47)	4 (15)	8 (33)
> 15	105 (61)	42 (49)	10 (45)	8 (42)	21 (81)	12 (50)
Patients with dactylitis at baseline, n (%)						
With dactylitis	62 (36)	31 (36)	11 (50)	10 (53)	ND	ND
Without dactylitis	111 (64)	55 (64)	11 (50)	9 (47)	ND	ND

Table 14: Characteristics of the study populations – RCT, indirect comparison: guselkumab vs. ustekinumab (research question 2) (multipage table)

Study Characteristics Category	Studies with guselkumab				Study with ustekinumab	
	COSMOS		DISCOVER 1		PSUMMIT 2	
	Guselkumab	Placebo	Guselkumab	Placebo	Ustekinumab	Placebo
	N[a] = 173	N[a] = 86	N[a] = 22	N[a] = 19	N[a] = 26	N[a] = 24
Patients with enthesitis at baseline, n (%)						
With enthesitis	118 (68)	56 (65)	11 (50)	14 (74)	ND	ND
Without enthesitis	55 (32)	30 (35)	11 (50)	5 (26)	ND	ND
PASI score at baseline, n (%)						
< 12	108 (62)	57 (66)	15 (68)	13 (68)	ND	ND
≥ 12 to < 20	29 (17)	18 (21)	3 (14)	2 (11)	ND	ND
≥ 20	35 (20)	11 (13)	4 (18)	4 (21)	ND	ND
Unknown	1 (1)	0 (0)	0 (0)	0 (0)	ND	ND
Number of previous TNF inhibitors, n (%)						
1	155 (90)	75 (87)	17 (77)	17 (89)	ND	ND
2	18 (10)	11 (13)	5 (23)	2 (11)	ND	ND
Reason for discontinuation of previous therapy with TNF inhibitors, n (%)						
Lack of efficacy	144 (83)	69 (80)	13 (59)	10 (53)	ND	ND
Other reason	22 (13)	15 (17)	8 (36)	7 (37)	ND	ND
Not applicable	7 (4)	2 (2)	1 (5)	2 (11)	ND	ND
Concomitant therapy with MTX at baseline, n (%)						
Yes	104 (60)	50 (58)	16 (73)	14 (74)	26 (100)	24 (100)
No	69 (40)	36 (42)	6 (27)	5 (26)	0 (0)	0 (0)

Table 14: Characteristics of the study populations – RCT, indirect comparison: guselkumab vs. ustekinumab (research question 2) (multipage table)

Study Characteristics Category	Studies with guselkumab				Study with ustekinumab	
	COSMOS		DISCOVER 1		PSUMMIT 2	
	Guselkumab	Placebo	Guselkumab	Placebo	Ustekinumab	Placebo
	N[a] = 173	N[a] = 86	N[a] = 22	N[a] = 19	N[a] = 26	N[a] = 24
Number of previous non-biologic DMARDs, n (%)						
None	12 (7)	5 (6)	1 (5)	0 (0)	0 (0)	0 (0)
1–2	ND	ND	ND	ND	22 (85)	21 (88)
1	116 (67)	55 (64)	9 (41)	11 (58)	ND	ND
2	33 (19)	21 (24)	10 (45)	2 (11)	ND	ND
≥ 3	12 (7)	5 (6)	2 (9)	6 (32)	4 (15)	3 (13)
Concomitant therapy with oral corticosteroids at baseline, n (%)						
Yes	30 (17)	17 (20)	3 (14)	5 (26)	9 (35)	5 (21)
No	143 (83)	69 (80)	19 (86)	14 (74)	17 (65)	19 (79)
Concomitant therapy with NSAIDs at baseline, n (%)						
Yes	93 (54)	44 (51)	16 (73)	12 (63)	17 (65)	18 (75)
No	80 (46)	42 (49)	6 (27)	7 (37)	9 (35)	6 (25)
Treatment discontinuation, n (%)	13 (8)	9 (10)	0 (0)	6 (32)	1 (4)	6 (25)
Early escape at week 16, n (%)	36 (21)	41 (48)	2 (9)	6 (32)	3 (12)	6 (25)
Study discontinuation, n (%)	ND	ND	ND	ND	ND	ND

a. Number of analysed patients.

DMARD: disease-modifying antirheumatic drug; F: female; M: male; MTX: methotrexate; n: number of patients in the category, N: number of randomized patients; ND: no data; NSAID: nonsteroidal anti-inflammatory drug; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; TNF: tumour necrosis factor; vs.: versus

The characteristics of the patients are largely comparable between the studies and also between the arms of a study. Isolated fluctuations between the studies and also between the arms of a study can probably be explained by the small size of the relevant subpopulations, especially in the studies DISCOVER 1 and PSUMMIT 2. The majority of the patients were between 45 and 65 years old, the age group of patients over 65 years was only represented by individuals except for the COSMOS study. The proportion of men and women was roughly balanced, although with a clear excess of female patients in one arm each of the studies DISCOVER 1 and PSUMMIT 2.

Module 4 of the dossier provided only incomplete information on family origin and origin of the study participants. There is no information for the COSMOS study. About half of the participants in the DISCOVER 1 study came from Eastern Europe, the others from Western Europe and North America, and in the PSUMMIT 2 study in about equal proportions from Europe and North America. In both studies, almost all patients were of white family origin.

The vast majority of patients had been ill for more than 3 years. The most common clinical picture was polyarticular arthritis with the absence of rheumatoid nodules, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis. In contrast to the other studies, DISCOVER 1 included almost 50% of patients with arthritis mutilans. The swollen joint count was < 10 in more than half of the patients, whereas tender joint count was > 15 in partly notably more than half of the cases. The studies COSMOS and DISCOVER 1 included both patients with dactylitis and those with enthesitis (PSUMMIT 2: no data).

All patients were pretreated with at least one TNF inhibitor. Treatment was mostly discontinued due to lack of efficacy; no data on intolerance are available. It cannot be inferred from the information in the dossier whether patients who discontinued prior therapy with biologics due to intolerance are possibly included in “other reason”. There is no information at all for the PSUMMIT 2 study. Thus, it is not fully comprehensible whether all patients correspond to the approval population. Almost all patients were also pretreated with csDMARDs. Concomitant therapy with MTX at baseline was common (up to over 70%), and mandatory in the PSUMMIT 2 study. In addition, 20 to 30% of the patients were treated with oral corticosteroids at baseline, and 50 to 70% with NSAIDs.

2.4.1.3 Similarity of the studies for the indirect comparison

Treatment duration and observation period

The company presented a data cut-off at 24 weeks for all 3 studies. The observation period of the patients is thus identical in all studies.

Similarity of the common comparator

At baseline, there was comparability of the placebo arms in the 3 studies. However, the early escape strategy calls the comparability into question, as the 2 studies on guselkumab included a switch from placebo to guselkumab (COSMOS) or start or dose increase of concomitant

therapy (DISCOVER 1), whereas the PSUMMIT 2 study included a switch to ustekinumab. Details on the consequences of the early escape strategy can be found in Section 2.4.1.5.

Similarity of the study populations

The demographic and clinical characteristics of the patients included were mostly comparable between the studies. Differences existed in particular in the expression of psoriatic arthritis according to subtype: In the COSMOS study, 31% of the patients had polyarticular arthritis with the absence of rheumatoid nodules, in DISCOVER 1 almost none, and in PSUMMIT 2 50%. Arthritis mutilans, in contrast, occurred almost exclusively in the DISCOVER 1 study. Spondylitis with peripheral arthritis was slightly more frequent in the COSMOS study than in the other 2 studies. Dactylitis occurred in about half of the participants in the DISCOVER 1 study, and in only 36% in the COSMOS study; data on PSUMMIT 2 were missing in the dossier.

For the COSMOS study, there was no information in the company's dossier on the participants' family origin and their origin by region. For the PSUMMIT 2 study, there were no data on the number of patients with enthesitis, dactylitis, prior therapy with TNF inhibitors and reason for discontinuation of this pretreatment. In the COSMOS study, lack of efficacy was given as the reason for discontinuing the prior therapy for slightly more than 80% of the patients, and for 56% in the DISCOVER 1 study.

All patients in the PSUMMIT 2 study received concomitant therapy with MTX, in the other 2 studies the proportion was 59% and 74% respectively.

The observed differences do not fundamentally call into question the possibility of an indirect comparison, but this cannot be used for the benefit assessment for other reasons.

Summary of the similarity

The studies COSMOS, DISCOVER 1 and PSUMMIT 2 show no major differences in terms of the patients included, so that these are considered sufficiently similar. However, due to the different early escape strategies at week 16, sufficient similarity between the common comparators no longer existed after this time point (see also Section 2.4.1.2). However, the indirect comparison conducted by the company is not suitable for the benefit assessment also for other reasons (see Section 2.4.1.5). The homogeneity assumption of the 2 included studies on guselkumab was therefore not checked.

2.4.1.4 Transferability of the study results to the German health care context

The company assumed that the included studies provide robust results with regard to the German health care context. It justified this with the fact that all 3 studies were also conducted in Germany, that more than 90% of the relevant subpopulations were of white family origin and that guselkumab and ustekinumab were used in compliance with the approval.

Although the PSUMMIT 2 study had been conducted several years earlier than the studies on guselkumab, the company did not assume that the management of the disease had changed between 2012 and 2019 or 2020 to such an extent that the transferability of the results of the PSUMMIT 2 study to the current context is questionable. It conceded, however, that there have been developments in health care during this period, so that a risk of bias in the context of the indirect comparison cannot be ruled out.

From the company's point of view, there are overall no restrictions that would fundamentally argue against transferability to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4.1.5 Risk of bias across outcomes (study level)

Table 15 shows the risk of bias across outcomes (risk of bias at study level).

Table 15: Risk of bias across outcomes (study level) – RCT, indirect comparison: guselkumab vs. ustekinumab

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			
COSMOS	Yes	Yes	Yes	Yes	Yes	No[a]	High
DISCOVER 1	Yes	Yes	Yes	Yes	Yes	Yes	Low
PSUMMIT 2	Yes	Yes	Yes	Yes	Yes	No[a]	High

a. High proportion of patients switching from the control arm to the intervention arm at week 16 (COSMOS: 47.7%; PSUMMIT 2: 25.0%). This affects all outcomes.

RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as high for the studies COSMOS and PSUMMIT 2. This deviates from the assessment of the company, which assumed a low risk of bias for both studies. The assessment of the DISCOVER 1 study is consistent with that of the company.

Indirect comparison not usable due to high risk of bias

The results of the adjusted indirect comparison presented by the company are not usable for the benefit assessment; this is justified below.

Results from adjusted indirect comparisons have a low certainty of results per se. Only adjusted indirect comparisons of high methodological quality and with a sufficient number of studies with low risk of bias, in which a valid check of the assumption of homogeneity and consistency has been carried out, can be considered as having a moderate certainty of results. If there is only one study with a high risk of bias for one side of the included indirect comparison for an adjusted indirect comparison using an adequate common comparator, no hint of an added benefit or greater/lesser harm is regularly derived.

The risk of bias across outcomes was rated as high both for the results of the COSMOS study and for those of the PSUMMIT 2 study. This was due to the high proportion of patients in the placebo arm who switched to treatment with guselkumab or ustekinumab due to non-response at week 16 (early escape). For example, at the relevant time of analysis (week 24), 48% of patients in the placebo arm in the COSMOS study had switched to guselkumab, and 25% of patients in the placebo arm in the PSUMMIT 2 study had switched to ustekinumab. All patient-relevant outcomes are affected by the risk of bias.

Since there is therefore only one study with moderate certainty of results on the side of the direct comparison of ustekinumab with the common comparator placebo (study PSUMMIT 2) in the adjusted indirect comparison, the uncertainty in the available data is overall too high to be able to derive valid conclusions on the added benefit or greater/lesser harm of guselkumab in comparison with the ACT. Irrespective of the limitations described, the indirect comparison did not show a statistically significant difference between guselkumab and ustekinumab for any of the outcomes included by the company.

This deviates from the assessment of the company, which assessed the risk of bias across outcomes as low for both studies and did not address the treatment switch as biasing aspect on an outcome-specific basis.

2.4.2 Results on added benefit

The company identified no study of direct comparison on the added benefit in comparison with ustekinumab. Instead, it presented an adjusted indirect comparison with 3 studies using the common comparator placebo. However, particularly the only study on the ustekinumab side (PSUMMIT 2) has limited informative value due to the high number of patients in the placebo arm who switched to ustekinumab treatment after only 16 weeks. As there are no other studies comparing ustekinumab versus placebo, the indirect comparison conducted by the company is not usable. Hence, the company's dossier did not contain any relevant data on the added benefit of guselkumab in comparison with the ACT.

In summary, there is no hint of an added benefit of guselkumab in comparison with the ACT. An added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

The company did not present any data suitable for the derivation of an added benefit in patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior bDMARD therapy. An added benefit of guselkumab in comparison with the ACT is therefore not proven.

This corresponds to the assessment of the company, which used the adjusted indirect comparison but also did not derive an added benefit of guselkumab on the basis of the results.

2.5 Probability and extent of added benefit – summary

Table 16 shows a summary of probability and extent of the added benefit of guselkumab.

Table 16: Guselkumab – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy[b]	A TNF-alpha antagonist (**adalimumab** or certolizumab pegol or etanercept or golimumab or infliximab) or an IL-17 inhibitor (ixekizumab), possibly in combination with methotrexate	Added benefit not proven
Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior biologic disease-modifying antirheumatic drug (bDMARD) therapy	Switch to another biologic disease-modifying antirheumatic (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab or **ustekinumab**), possibly in combination with methotrexate	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. The patient population considered for research question 1 consists of bDMARD-naive patients.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; IL17: interleukin-17

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

References for English extract

Please see full dossier assessment for full reference list.

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

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