IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Guselkumab (plaque psoriasis) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Guselkumab (Plaque-Psoriasis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 February 2018). 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.

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSA	body surface area
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)
MCS	Mental Component Summary
MI	multiple imputation
MMRM	mixed-effects model repeated measures
NAPSI	Nail Psoriasis Severity Index
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PSSD	Psoriasis Symptoms and Signs Diary
PUVA	psoralen and ultraviolet-A light
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
sPGA	static Physician Global Assessment
ss-IGA	Scalp-specific Investigator Global Assessment

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 was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 23 November 2017.

Research question

Table 2: Research questions of the benefit assessment of guselkumab

Research question	Subindication	ACT[a]
A	Adult patients with moderate to severe plaque psoriasis who are candidates for systemic treatment[b]	**Fumaric acid esters** or ciclosporin or methotrexate or phototherapy (balneo-phototherapy, oral PUVA, NB-UVB) or secukinumab[c]
B	Adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or oral PUVA, or with contraindication or intolerance to such treatments	**Adalimumab** or infliximab or ustekinumab or secukinumab[c]

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 population includes all patients in the approved therapeutic indication, except for the patients mentioned in research question B.
c: The respective approval of the drugs is to be considered. Dosage of the ACT was to concur with the recommendations of the relevant SPC. A dose-fair comparison under exhaustion of the approval-compliant dosage (if tolerated) was to be conducted. It is a precondition that topical treatment alone is inadequate for the patients treated.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); PUVA: psoralen and ultraviolet-A light; SPC: Summary of Product Characteristics

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

- research question A: adult patients who are candidates for systemic treatment
- research question B: adult patients with inadequate response to other systemic treatments or who are unsuitable for these treatments

The company followed the G-BA's specification of the appropriate comparator therapy (ACT) for both research questions. From the options mentioned by the G-BA, the company chose fumaric acid esters for research question A and adalimumab for research question B.

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

Results for research question A: adult patients who are candidates for systemic treatment

Following the company, the RCT POLARIS was included for the assessment of the added benefit of guselkumab for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic treatment.

Study design

The POLARIS study was a randomized, multicentre, open-label study on the comparison of guselkumab with fumaric acid esters. The study included adults with moderate to severe plaque psoriasis who had not yet received systemic treatment. The study defined the severity grade of the psoriasis using a Psoriasis Area and Severity Index (PASI) > 10, or an affected body surface area (BSA) of > 10% and a Dermatology Life Quality Index (DLQI) of > 10.

The POLARIS study had 2 phases. In the first study phase (main study), 119 patients were randomly allocated in a 1:1 ratio to both study arms: 60 patients to the guselkumab arm, and 59 patients to the fumaric acid ester arm. In the main study, treatment with guselkumab or fumaric acid esters was to be conducted for 24 weeks. Only patients who had not discontinued their treatment during the main study and who had not received any prohibited medications were allowed to participate in the second study phase. According to the company, the results on this study phase were not available. Hereinafter, this second study phase is not considered further.

Both the administration of guselkumab and the administration of fumaric acid esters were without relevant deviations from the Summaries of Product Characteristics (SPCs).

Primary outcome of the study was the PASI 90; patient-relevant secondary outcomes were all-cause mortality, remission (PASI 100), outcomes on symptoms, health-related quality of life and side effects. In the first study phase, the outcomes included were recorded for a maximum of 24 weeks (or 32 weeks if the patients did not participate in the second study phase).

Risk of bias and overall assessment of the certainty of conclusions

The risk of bias at study level for the POLARIS study was rated as low. At outcome level, the risk of bias was rated as high for all outcomes except for the outcome “all-cause mortality”.

Due to the high risk of bias at outcome level and due to the presence of only one study, at most hints, e.g. of an added benefit, can initially be derived for all outcomes, except for all-cause mortality. However, since the effects regarding the outcomes “remission” (PASI 100), “discontinuation due to adverse events (AEs)” and “flushing” were very large, indications for these outcomes are derived below.

Mortality

All-cause mortality

No deaths occurred in the POLARIS study up to week 24. There was no hint of an added benefit of guselkumab in comparison with fumaric acid esters for all-cause mortality; an added benefit is therefore not proven.

Morbidity

Remission (PASI 100)

For the outcome "remission", recorded with the PASI 100, a statistically significant difference in favour of guselkumab was shown in comparison with fumaric acid esters. There was a high risk of bias for this outcome. Considering the size of the observed effect, however, it was not assumed that the effect and the extent of the effect were caused by systematic bias alone. Overall, this resulted in an indication of an added benefit of guselkumab in comparison with fumaric acid esters for the outcome "remission" (PASI 100).

Patient-reported symptoms (PSSD)

The company presented no data for the outcome "patient-reported symptoms" (Psoriasis Symptoms and Signs Diary [PSSD]). The study documents also did not contain the results on this outcome without providing an explanation. There was no hint of an added benefit of guselkumab in comparison with fumaric acid esters for patient-reported symptoms (PSSD); an added benefit is therefore not proven.

No psoriasis symptoms on the scalp (ss-IGA 0)

The company presented no data for the outcome "no psoriasis symptoms on the scalp" (Scalp-specific Investigator Global Assessment [ss-IGA 0]). The study documents also did not contain the results on this outcome without providing an explanation. There was no hint of an added benefit of guselkumab in comparison with fumaric acid esters for the outcome "no psoriasis symptoms on the scalp" (ss-IGA 0); an added benefit is therefore not proven.

Health-related quality of life

DLQI (0 or 1)

A statistically significant difference in favour of guselkumab in comparison with fumaric acid esters was shown for the outcome "DLQI (0 or 1)". Under consideration of the high risk of bias, there was a hint of an added benefit of guselkumab in comparison with fumaric acid esters.

SF-36

For the Short Form (36) Health Survey (SF-36), the Physical Component Summary (PCS) and the Mental Component Summary (MCS) were considered individually. The mean difference of the change from the start of the study until treatment week 24 was considered in each case.

The consideration of the mean differences showed no statistically significant difference between the treatment arms for the MCS. This resulted in no hint of an added benefit of

guselkumab in comparison with fumaric acid esters; an added benefit for the outcome "MCS" is therefore not proven.

A statistically significant difference in favour of guselkumab in comparison with fumaric acid esters was shown for PCS, however. The confidence interval (CI) for the standardized mean difference (SMD) was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. Under consideration of the high risk of bias, there was a hint of an added benefit of guselkumab in comparison with fumaric acid esters for PCS.

Side effects

Serious adverse events

There was no statistically significant difference between the treatment arms for the outcome "serious adverse events (SAEs)". Hence for the outcome "SAEs", there was no hint of greater or lesser harm from guselkumab in comparison with fumaric acid esters; greater or lesser harm is therefore not proven.

Discontinuation due to adverse events

A statistically significant difference in favour of guselkumab in comparison with fumaric acid esters was shown for the outcome "discontinuation due to AEs". There was a high risk of bias also for this outcome. Considering the size of the observed effect, however, it was not assumed that the effect and the extent of the effect were caused by systematic bias alone. Overall, this resulted in an indication of lesser harm of guselkumab in comparison with fumaric acid esters for discontinuations due to AEs.

Specific adverse events

Infections and infestations

No statistically significant difference between the treatment arms was shown for the outcome "infections and infestations". Hence for infections and infestations, there was no hint of greater or lesser harm from guselkumab in comparison with fumaric acid esters; greater or lesser harm is therefore not proven.

Gastrointestinal disorders

A statistically significant difference in favour of guselkumab in comparison with fumaric acid esters was shown for the outcome "gastrointestinal disorders". Under consideration of the high risk of bias, there was a hint of lesser harm of guselkumab in comparison with fumaric acid esters for gastrointestinal disorders.

Flushing

A statistically significant difference in favour of guselkumab in comparison with fumaric acid esters was shown for the outcome "flushing". There was a high risk of bias also for this outcome. Considering the size of the observed effect, however, it was not assumed that the effect and the extent of the effect were caused by systematic bias alone. Overall, this resulted

in an indication of lesser harm of guselkumab in comparison with fumaric acid esters for the outcome “flushing”.

Results for research question B: adult patients with inadequate response to other systemic treatments or who are unsuitable for these treatments

Following the company, the RCTs VOYAGE 1 and VOYAGE 2 were included for the assessment of the added benefit of guselkumab for the treatment of adults with moderate to severe plaque psoriasis with inadequate response to other systemic treatment or who are unsuitable for these treatments.

Study design

The studies VOYAGE 1 and VOYAGE 2 were randomized, double-blind, multicentre studies on the comparison of guselkumab versus adalimumab and placebo.

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 following study arms: guselkumab (VOYAGE 1: N = 329; VOYAGE 2: N = 496), placebo (VOYAGE 1: N = 174; VOYAGE 2: N = 248), and adalimumab (VOYAGE 1: N = 334; VOYAGE 2: N = 248). Randomization was stratified by study centres in both studies.

The studies included adults 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. In both studies, the inclusion criteria were not restricted to patients of the present research question B, i.e. patients with inadequate response to systemic treatment (including ciclosporin, methotrexate and psoralen and ultraviolet-A light [PUVA]) or with intolerance or contraindication to such treatment. The company therefore presented the results of a subpopulation (see below). Both studies defined disease severity using the following criteria: BSA $\geq$ 10%, PASI $\geq$ 12, and static Physician Global Assessment (sPGA) $\geq$ 3. The company further restricted its subpopulation for the benefit assessment by excluding patients with a DLQI $\leq$ 10 (see below).

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) and an open-label extension phase.

In both studies, treatment with guselkumab and adalimumab was largely in line with the corresponding SPC.

Primary outcomes of both studies were PASI 90 and an Investigator Global Assessment (IGA) score of 0 or 1. Relevant secondary outcomes were all-cause mortality, remission (PASI 100), outcomes on symptoms, health-related quality of life and side effects. The meta-analyses for week 24 (or week 28 for side effects) were used for the benefit assessment.

Subpopulation relevant for the benefit assessment

Concurring with the G-BA's specification, only subpopulations of the studies VOYAGE 1 and VOYAGE 2 were relevant for answering research question B, namely those patients for whom systemic drug treatment is inadequate or contraindicated or who do not tolerate such treatment. The captions of the additional analyses conducted for the company's dossier show that the company excluded those patients who had not received systemic treatment ("exclude treatment naive") for forming the subpopulation from the studies. It could not be inferred from the information in the additional analyses whether the subpopulation formed by the company was composed of all pretreated patients who had already received systemic treatment and who, in accordance with the G-BA's definition of the subpopulation, also had discontinued their prior therapy for the reasons stated above. It is also possible that the subpopulation formed by the company was composed of all patients with prior systemic therapy, irrespective of the reason for their discontinuation of the prior therapy. The latter would be inadequate as, according to the study documents, the studies also included patients who had discontinued their prior systemic therapy for reasons other than inadequate response, contraindication or intolerance. If the company's subpopulation included patients who had switched treatment for other reasons, their proportion could be larger than 20%. The exact composition of the subpopulation formed by the company cannot be inferred from the patient characteristics presented by the company in the dossier. One of the reasons for this is that, at the same time, the company excluded patients with a DLQI ≤ 10 at the start of the study (see below). It therefore remains unclear overall whether the company implemented its intention to only include patients with inadequate response, contraindication or intolerance to systemic therapies.

As described above, the company further restricted its population by excluding patients with a DLQI ≤ 10 from the study population of both studies. No uniform criteria exist for the definition of the severity of psoriasis. Both the criteria defined a priori in the VOYAGE studies and the company's criteria for the benefit assessment (under consideration of the DLQI) were a sufficient representation of moderate to severe plaque psoriasis. In addition, the company provided no explanation for excluding patients with a DLQI ≤ 10 from the study population. Hence the reasons for the company's unnecessary post hoc restriction of its subpopulation are overall unclear. The patients excluded by the company based on the DLQI constituted about 30% of the total population of the studies with the proportion in relation to the subpopulation of interest being unclear.

The subpopulation used for the assessment of research question B was about 45.6% (VOYAGE 1) and 54.2% (VOYAGE 2) of the patients randomized to the guselkumab arm, and 50.0% (VOYAGE 1) and 53.2% (VOYAGE 2) of the patients randomized to the adalimumab arm. It comprised n = 150 (VOYAGE 1) and n = 269 (VOYAGE 2) patients in the guselkumab arm, and n = 167 (VOYAGE 1) and n = 132 (VOYAGE 2) patients in the adalimumab arm.

Both uncertainties in the company's formation of the subpopulation were considered in the derivation of the certainty of conclusions of the results (see below).

Risk of bias and overall assessment of the certainty of conclusions

The risk of bias at study level for the studies VOYAGE 1 and VOYAGE 2 was rated as low.

No data were available for the outcomes "no psoriasis symptoms on the scalp" (ss-IGA 0) and "no psoriasis symptoms on the hands and feet" (Physician Global Assessment of Hands and/or Feet (hf-PGA). Hence the risk of bias was not assessed for these outcomes. The risk of bias of the results for all other outcomes was rated as low, except for patient-reported symptoms (PSSD) and no psoriasis symptoms on the nails (Nail Psoriasis Severity Index [NAPSI] 0).

Due to the uncertainties regarding the company's formation of the subpopulation, at most indications, e.g. of an added benefit, were derived from the meta-analysis of the studies VOYAGE 1 and VOYAGE 2. In addition, there was a high risk of bias due to the large or unknown proportion of imputed values or potentially informative censoring for the outcomes "PSSD" and "no psoriasis symptoms on the fingernails" (NAPSI 0). This problem was addressed with sensitivity analyses conducted by the Institute in the analyses on the proportion of patients with event. In case of a robust result, an indication, e.g. of an added benefit, was derived for this result despite the high risk of bias. In other cases, no more than a hint was derived.

Mortality

All-cause mortality

No deaths occurred in the studies VOYAGE 1 and VOYAGE 2 until treatment week 24. There was no hint of an added benefit of guselkumab in comparison with adalimumab for all-cause mortality; an added benefit is therefore not proven.

Morbidity

Remission (PASI 100)

Regarding the outcome "remission", determined with PASI 100, the meta-analysis of the studies showed a statistically significant effect in favour of guselkumab both in the proportion of patients who achieved remission by week 24 and in the analysis of the time to remission.

In view of the reduced certainty of conclusions of the results, there was an indication of an added benefit of guselkumab compared with adalimumab for remission (PASI 100) for each of both analyses.

Patient-reported symptoms (PSSD)

The Symptom score 0 and the Sign score 0 were considered individually for the PSSD. Both the proportions of patients with a Symptom or Sign score of 0 at week 24 and the time to achieving a Symptom or Sign score of 0 were considered. Regarding the Symptom score 0 and the Sign score 0, both analyses showed statistically significant differences in favour of guselkumab in the meta-analysis.

However, the results from the analyses using the proportions of the patients with Symptom score 0 or Sign score 0 were highly biased due to the large proportion of imputed values. For this reason, results of sensitivity analyses conducted by the Institute were additionally considered for the responder analyses at week 24. The result of these analyses continued to show a statistically significant difference in favour of guselkumab both for the Symptom and the Sign score 0, despite reduced effect size. Hence the result was robust.

In view of the reduced certainty of conclusions of the results, there was an indication of an added benefit of guselkumab versus adalimumab for the proportion of patients with PSSD Symptom score 0 and PSSD Sign score 0.

There was a hint of an added benefit of guselkumab versus adalimumab for results from the analysis using the time to achieving a PSSD Symptom score 0 and a PSSD Sign score 0.

No psoriasis symptoms on the scalp (ss-IGA 0)

The company presented no data for the outcome "no psoriasis symptoms on the scalp" (ss-IGA 0) for the relevant subpopulation. There was no hint of an added benefit of guselkumab in comparison with adalimumab for no psoriasis symptoms on the scalp (ss-IGA 0); an added benefit is therefore not proven.

No psoriasis symptoms on hands and feet (hf-PGA 0)

The company presented no analyses for the outcome "no psoriasis symptoms on the hands and feet" (hf-PGA 0) for the relevant subpopulation. There was no hint of an added benefit of guselkumab in comparison with adalimumab for the outcome "no psoriasis symptoms on the hands and feet" (hf-PGA 0); an added benefit is therefore not proven.

No psoriasis symptoms on the nails (NAPSI 0)

In the course of the study, the outcome "no psoriasis symptoms on the nails" was only recorded in patients who had nail psoriasis at the start of the study. For the outcome "no psoriasis symptoms on the nails" (NAPSI 0), the meta-analysis of the studies showed no statistically significant difference between the treatment arms for this patient group regarding both the analysis of the proportion of patients with NAPSI 0 and for the time to achieving NAPSI 0. Consequently, there was no hint of an added benefit of guselkumab in comparison with adalimumab for NAPSI 0; an added benefit is therefore not proven.

Health-related quality of life

DLQI (0 or 1)

For health-related quality of life, measured with the DLQI, the meta-analysis of the studies produced a statistically significant difference in favour of guselkumab both for the proportion of patients with a DLQI of 0 or 1 and for the time to achieving a DLQI of 0 or 1.

In view of the reduced certainty of conclusions of the results, there was an indication of an added benefit of guselkumab compared with adalimumab for health-related quality of life, measured with the DLQI (0 or 1) for each of both analyses.

SF-36

The PCS and the MCS of the SF-36 were considered individually. The mean difference of the change from the start of the study until week 24 of the VOYAGE 2 study was considered for each summary score. The VOYAGE 1 study did not record health-related quality of life using the SF-36. A statistically significant difference was shown for the mean difference both of the PCS and of the MCS. The CI for the SMD was not fully outside the irrelevance range [−0.2; 0.2], however. It could therefore not be inferred that the effect was relevant. This resulted in no hint of an added benefit of guselkumab in comparison with adalimumab for the SF-36; an added benefit is therefore not proven.

Side effects

Serious adverse events and discontinuation due to adverse events

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

Specific adverse events

Infections and infestations

The meta-analysis of the studies showed no statistically significant difference between the treatment groups for the outcome “infections and infestations”. Hence for the outcome “infections and infestations”, there was no hint of greater or lesser harm from guselkumab in comparison with adalimumab; greater or lesser harm is therefore not proven.

If applicable, further specific adverse events

A conclusive choice of further specific AEs based on the data provided in the dossier was not possible. It can only be excluded that potential specific AEs were serious or resulted in discontinuation of treatment. Hence there was no hint of greater or lesser harm from guselkumab in comparison with adalimumab; greater or lesser harm is therefore not proven.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug guselkumab compared with the ACT for each research question is assessed as follows:

Research question A: adult patients who are candidates for systemic treatment

Overall, there were only positive effects of different certainty of results (indication or hint) for guselkumab in comparison with fumaric acid esters in the outcome categories of morbidity, health-related quality of life and side effects. The extent of the effects ranged from "considerable" to "major" or was "non-quantifiable".

It must be taken into account in the overall consideration that the company's dossier (including Module 5) presented no results for the assessment of patient-reported symptoms (PSSD) and no psoriasis symptoms on the scalp (ss-IGA 0), although these were planned to be recorded and analysed in the study.

In summary, there is an indication of considerable added benefit of guselkumab in comparison with fumaric acid esters for adult patients with moderate to severe plaque psoriasis who are candidates for systemic treatment.

Research question B: adult patients with inadequate response to other systemic treatments or who are unsuitable for these treatments

The final consideration of the data for adults with inadequate response to other systemic treatments or who are not candidates for these treatments showed only positive effects of guselkumab in comparison with adalimumab in the outcome categories of morbidity and health-related quality of life, each with the probability "indication". In each case, the extent was considerable or non-quantifiable.

No analyses for the relevant subpopulation were available for the assessment of the morbidity outcomes of no psoriasis symptoms on the scalp and no psoriasis symptoms on the hands and feet. There were also no complete data for the choice of further specific AEs. However, it can be excluded that potential specific AEs were serious or resulted in discontinuation of treatment.

Nonetheless, due to the notable positive effects of guselkumab – particularly the effect size regarding remission (PASI 100) – it is not assumed in the present data situation that the presence of the missing information on the outcomes "no psoriasis symptoms on the scalp" or

[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].

"no psoriasis symptoms on the hands and feet" and on the further specific AEs would change the overall conclusion on the added benefit.

In summary, there is an indication of a considerable added benefit of guselkumab in comparison with adalimumab for adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or PUVA, or with contraindication or intolerance to such treatments.

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

Table 3: Guselkumab – probability and extent of added benefit

Research question	**Subindication**	**ACT**[a]	**Probability and extent of added benefit**
A	Adult patients with moderate to severe plaque psoriasis who are candidates for systemic treatment[b]	**Fumaric acid esters** or ciclosporin or methotrexate or phototherapy (balneo-phototherapy, oral PUVA, NB-UVB) or secukinumab[c]	Indication of considerable added benefit
B	Adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or PUVA, or with contraindication or intolerance to such treatments	**Adalimumab** or infliximab or ustekinumab or secukinumab[c]	Indication of considerable added benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The population includes all patients in the approved therapeutic indication, except for the patients mentioned in research question B.
c: Dosage of the ACT was to concur with the recommendations of the relevant SPC. A dose-fair comparison under exhaustion of the approval-compliant dosage (if tolerated) was to be conducted. It is a precondition that topical treatment alone is inadequate for the patients treated.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); PUVA: psoralen and ultraviolet-A light; SPC: Summary of Product Characteristics

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

2.2 Research question

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

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

Table 4: Research questions of the benefit assessment of guselkumab

Research question	Subindication	ACT[a]
A	Adult patients with moderate to severe plaque psoriasis who are candidates for systemic treatment[b]	**Fumaric acid esters** or ciclosporin or methotrexate or phototherapy (balneo-phototherapy, oral PUVA, NB-UVB) or secukinumab[c]
B	Adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or oral PUVA, or with contraindication or intolerance to such treatments	**Adalimumab** or infliximab or ustekinumab or secukinumab[c]

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 population includes all patients in the approved therapeutic indication, except for the patients mentioned in research question B.
c: The respective approval of the drugs is to be considered. Dosage of the ACT was to concur with the recommendations of the relevant SPC. A dose-fair comparison under exhaustion of the approval-compliant dosage (if tolerated) was to be conducted. It is a precondition that topical treatment alone is inadequate for the patients treated.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); PUVA: psoralen and ultraviolet-A light; SPC: Summary of Product Characteristics

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

- research question A: adult patients who are candidates for systemic treatment
- research question B: adult patients with inadequate response to other systemic treatments or who are unsuitable for these treatments

The company followed the G-BA's specification of the ACT for both research questions. From the options mentioned by the G-BA, the company chose fumaric acid esters for research question A and adalimumab for research question B.

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

2.3 Research question A: adult patients who are candidates for systemic treatment

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: 19 September 2017)
- bibliographical literature search on guselkumab (last search on 21 September 2017)
- search in trial registries for studies on guselkumab (last search on 19 September 2017)

To check the completeness of the study pool:

- search in trial registries for studies on guselkumab (last search on 4 December 2017)

The check identified no additional relevant study.

2.3.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: guselkumab vs. fumaric acid esters (research question A)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
CNTO1959PSO3008 (POLARIS[b])	No	Yes	No

a: Study sponsored by the company.
b: In the following tables, the study is referred to with this abbreviated form.
RCT: randomized controlled trial; vs.: versus

Section 2.3.4 contains a reference list for the studies included.

2.3.1.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: guselkumab vs. fumaric acid esters (research question A)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
POLARIS	RCT, open-label	Adults (≥ 18 years) with plaque psoriasis (PASI > 10 or BSA > 10 and DLQI > 10) for at least 6 months before study start without prior systemic therapy	Guselkumab (N = 60) fumaric acid esters (N = 59)	Screening: about 3 weeks Part I (main study): treatment: 24 weeks Part II (extension study)[b]: treatment: up to week 56[c] follow-up: up to week 64[d]	27 centres in Germany 12/2016–ongoing	Primary: PASI 90 Secondary: all-cause mortality, symptoms, health-related quality of life, AEs

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for this benefit assessment.
b: The first amendment to the protocol (25 April 2017) divided the study into 2 parts. Only patients who had not discontinued their treatment during the main study (part I) and who had not received any prohibited medications were allowed to participate in the second study phase (part II). According to the company, the results on this study phase were not available. This study phase is not presented in the following tables.
c: Between week 24 and week 32, treatment was with the medication originally allocated. After week 32, patients who had achieved PASI 75 continued their allocated treatment. Patients in the fumaric acid ester arm who had not achieved PASI 75 could be switched to treatment with guselkumab after week 32, whereas patients in the guselkumab arm could continue their treatment with guselkumab.
d: Patients who had only participated in the first part of the study were followed-up at most until week 32.
AE: adverse event; BSA: body surface area; DLQI: Dermatology Life Quality Index; N: number of randomized patients; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: guselkumab vs. fumaric acid esters (research question A)

Study	Intervention	Comparison	Concomitant treatment
POLARIS	Guselkumab 100 mg SC in week 0, 4, 12 and 20	Oral fumaric acid esters according to the following titration scheme: week 0: 1x 30 mg/day week 1: 2x 30 mg/day week 2: 3x 30 mg/day week 2[a]–3: 1x 120 mg/day week 4: 2x 120 mg/day week 5: 3x 120 mg/day week 6: 4x 120 mg/day week 7: 5x 120 mg/day week 8: 6x 120 mg/day[b] Interruption, slowdown or discontinuation of up-titration if one of the following reasons occurs: ▪ achieving the maximum dosage of 3x 2 tablets/day ▪ achieving PASI 90[d] ▪ Occurrence of side effects (e.g. gastrointestinal discomfort, redness); dosage increase in accordance with the titration scheme possible after side effects have subsided	<u>Concomitant treatment permitted:</u> ▪ shampoos containing tar or salicylic acid[c] ▪ topical moisturizer[c] ▪ NSAIDs and paracetamol ≤ 2 weeks in acute clinical phase ▪ 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 <u>Non-permitted concomitant treatment:</u> ▪ topical treatments that may influence the psoriasis (such as corticosteroids, tar, anthralin, calcipotriol, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, pimecrolimus, tacrolimus, traditional Taiwanese, Korean or Chinese substances) ▪ phototherapy up to week 24 ▪ systemic treatment for psoriasis ▪ systemic herbal agents or traditional Taiwanese, Korean or Chinese substances ▪ other biological or systemic drugs that may influence the psoriasis ▪ sulfasalazine, gold IM ▪ 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: Administration starts on the last day of week 2 directly after having taken a total of 40 tablets of 30 mg each.
b: Maximum dosage.
c: Not allowed on the day of the study visit.
d: After achieving PASI 90 response, it was at the investigator's discretion to reduce the dose in accordance with the required maintenance dose. It was recommended to verify the sustained PASI 90 response before dose reduction unless reduction was required due to intolerance. The dose could be maintained or increased further to achieve greater efficacy as long as the benefit-risk balance was considered positive. If the efficacy decreased after dose reduction, the dose could be increased again.

BCG: bacille Calmette-Guérin; IM: intramuscular; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; SC: subcutaneous; vs.: versus

Study design

The POLARIS study was a randomized, open-label study on the comparison of guselkumab with fumaric acid esters. The study is currently conducted in 27 study centres in Germany.

The study included adult patients with plaque psoriasis who had not yet received systemic treatment. Prior treatments with topical therapies must have been inadequate, or the patients had not tolerated these treatments, or they were no (longer) candidates for topical therapy alone due to the severity of their disease at the time point of study inclusion. The study defined the severity grade of the psoriasis using a PASI > 10, or an affected BSA of > 10% and a DLQI of > 10. For the present benefit assessment, this definition of the severity grade was rated as adequate representation of moderate to severe psoriasis (see Section 2.6.2.4.1 of the full dossier assessment). Overall, the population investigated in the POLARIS study corresponded to the therapeutic indication of guselkumab in the present research question.

The POLARIS study had 2 phases. In the first study phase (main study), 119 patients were randomly allocated in a 1:1 ratio to both study arms: 60 patients to the guselkumab arm, and 59 patients to the fumaric acid ester arm. In the main study, treatment with guselkumab or fumaric acid ester was to be conducted for 24 weeks. Only patients who had not discontinued their treatment during the main study and who had not received any prohibited medications were allowed to participate in the second study phase. According to the company, the results on this study phase were not available. Hereinafter, this second study phase is therefore not considered further.

The patients in the guselkumab arm received 100 mg subcutaneous guselkumab at week 0, 4, 12 and 20. This concurs with the requirements of the SPC [3]. According to the SPC of guselkumab, consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. This was not explicitly mandated in the study protocol, however, and was not addressed by the company in the dossier. It is assumed, however, that the missing note on possible treatment discontinuation had no relevant influence on the study results.

The patients in the fumaric acid ester arm received daily oral fumaric acid esters following a defined titration scheme (see Table 7), which started with a low dose, followed by a dose increase until reaching the treatment goal. The titration scheme complied with the requirements of the SPC [4]. The treatment goal was defined as a 90% improvement of the PASI (PASI 90). If the treatment goal was met, it was at the investigator's discretion to reduce, maintain or further increase the dose if the advantage for the patients was greater than the risk of AEs. If efficacy of the treatment decreased after dose reduction, the dose could be increased again.

Primary outcome of the study was the PASI 90; relevant secondary outcomes were all-cause mortality, remission (PASI 100), outcomes on symptoms, health-related quality of life and side effects. In the first study phase, the outcomes included were recorded for up to 24 weeks (or 32 weeks if the patients did not participate in the second study phase).

The present assessment was based on analyses of a planned interim analysis at week 24.

Characteristics of the study population

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

Table 8: Characteristics of the study population – RCT, direct comparison: guselkumab vs. fumaric acid esters (research question A)

Study Characteristics Category	Guselkumab	Fumaric acid esters
POLARIS	N[a] = 60	N[a] = 59
Age [years], mean (SD)	39.0 (14.0)	45.8 (13.7)
Sex [F/M], %	33.3/66.7	28.8/71.2
Ethnicity, n (%)		
White	57 (95.0)	57 (96.6)
Asian	2 (3.3)	0 (0)
Other[b]	1 (1.7)	2 (3.4)
Scalp involvement, n (%)	ND	ND
Face and neck involvement, n (%)	ND	ND
Fingernail involvement, n (%)	ND	ND
Genital involvement, n (%)	ND	ND
Duration of disease [years][c], mean (SD)	14.8 (11.7)	17.2 (13.9)
PASI, mean (SD)	16.7 (6.4)	18.3 (7.4)
PASI ≥ 20, n (%)	15 (25.0)	17 (28.8)
DLQI, mean (SD)	17.3 (4.4)	18.9 (5.1)
IGA[d], n (%)		
0 or 1 (clear or minimal)	0 (0)	1 (1.7)
2 (mild)	6 (10.0)	7 (11.9)
3 (moderate)	44 (73.3)	42 (71.2)
4 (severe)	10 (16.7)	9 (15.3)
Psoriatic arthritis, n (%)	ND	ND
Prior topical medication[e], n (%)	57 (95.0)	57 (96.6)
Treatment discontinuation, n (%)	4 (6.7)	23 (39.0)
Study discontinuation, n (%)	ND	ND

a: Number of randomized patients.
b: Institute's calculation, including black, multiple ethnicity, and other.
c: Time from first diagnosis of the psoriasis until randomization.
d: IGA records the physician's assessment of the severity of the signs of redness, thickness and scaling.
e: Except for shampoos and topical moisturizers.
DLQI: Dermatology Life Quality Index; F: female; IGA: Investigator Global Assessment; M: male, n: number of patients in the category; N: number of randomized patients; ND: no data; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patient characteristics were largely comparable between the treatment groups of the POLARIS study. Over 95% of the patients were white; their mean age was 39 years (guselkumab arm) and 46 years (fumaric acid ester arm). Most patients were men. The mean PASI score was 17 to 18, with a PASI score of ≥ 20 in about one quarter of the patients.

About 40% of the patients in the fumaric acid ester arm discontinued treatment in the course of the study. Occurrence of AEs was the main reason for treatment discontinuation. In comparison, only about 7% of the patients in the guselkumab discontinued treatment.

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: guselkumab vs. fumaric acid esters (research question A)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
POLARIS	Yes	Yes	No	No	No[a]	Yes	Low

a: The study documents presented no results for the outcomes “ss-IGA 0” and “PSSD” without providing an explanation.

PSSD: Psoriasis Symptoms and Signs Diary; RCT: randomized controlled trial; ss-IGA: Scalp-specific Investigator Global Assessment; vs.: versus

The risk of bias at study level was rated as low for the included study. This concurs with the company’s assessment.

Limitations resulting from the open-label study design are described with the outcome-specific risk of bias in Section 2.3.2.2. The missing results on the outcomes “no psoriasis symptoms on the scalp (ss-IGA 0)” and “PSSD” were considered in the overall consideration of the results (see Section 2.3.3.2).

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - remission (PASI 100)
  - patient-reported symptoms (PSSD)
  - no psoriasis symptoms on the scalp (ss-IGA 0)
- Health-related quality of life
  - DLQI (0 or 1)
  - SF-36
- Side effects
  - SAEs
  - discontinuation due to AEs
  - infections and infestations (System Organ Class [SOC])
  - if applicable, further specific AEs

Analyses at week 24 were used for the benefit assessment. The choice of patient-relevant outcomes deviated from that of the company, which, on the one hand, did not include the outcomes “patient-reported symptoms (PSSD)” and “no psoriasis symptoms on the scalp (ss-IGA 0)” in the dossier (Module 4 A), and, on the other, used further outcomes (see Section 2.6.2.4.3 of the full dossier assessment).

The company presented different analyses for the outcomes it used. The present benefit assessment used analyses using the time to first event for the outcomes of remission (PASI 100), DLQI (0 or 1) and SAEs. Analyses on the mean change of values imputed with multiple imputation (MI) were used for health-related quality of life measured with the SF-36. Analyses using the proportion of patients with event were used for the outcomes of all-cause mortality, discontinuation due to AEs, and specific AEs (see also Section 2.6.2.4.3 of the full dossier assessment).

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

Table 10: Matrix of outcomes – RCT, direct comparison: guselkumab vs. fumaric acid esters (research question A)

Study	Outcomes										
	All-cause mortality	Remission (PASI 100)[a]	Patient-reported symptoms (PSSD)	No psoriasis symptoms on the scalp (ss-IGA 0)	Health-related quality of life (DLQI 0 or 1)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Infections and infestations (SOC)	Gastrointestinal disorders (SOC)	Flushing (PT)
POLARIS (24 weeks)	Yes	Yes	No[b]	No[b]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: Improvement in score by 100% compared with the start of the study.
b: The company did not include the outcome in its assessment and presented no analyses (see Section 2.6.2.4.3 of the full dossier assessment).

AE: adverse event; DLQI: Dermatology Life Quality 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; SOC: System Organ Class; ss-IGA: Scalp-specific Investigator Global Assessment; vs.: versus

2.3.2.2 Risk of bias

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

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: guselkumab vs. fumaric acid esters (research question A)

Study	Study level	Outcomes										
		All-cause mortality	Remission (PASI 100)[a]	Patient-reported symptoms (PSSD)	No psoriasis symptoms on the scalp (ss-IGA 0)	Health-related quality of life (DLQI 0 or 1)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Infections and infestations (SOC)	Gastrointestinal disorders (SOC)	Flushing (PT)
POLARIS (24 weeks)	L	L	H[b]	-[c]	-[c]	H[b, d]	H[d, e]	H[b]	H[d]	H[f, d]	H[f, d]	H[f, d]

a: Improvement in score by 100% compared with the start of the study.
b: Potential informative censoring.
c: The company did not include the outcome in its assessment and presented no analyses (see Section 2.6.2.4.3 of the full dossier assessment).
d: Subjective outcome in open-label study design.
e: Large proportion or large difference between the treatment groups regarding the proportion of patients imputed using multiple imputation (guselkumab arm: 7% each for PCS and MCS vs. fumaric acid ester arm: 42% for PCS and 41% for MCS).
f: Large proportion of patients with incomplete observation (at least 7% guselkumab vs. 29% fumaric acid esters).
AE: adverse event; DLQI: Dermatology Life Quality Index; H: high; L: low; 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; SOC: System Organ Class; ss-IGA: Scalp-specific Investigator Global Assessment; vs.: versus

The risk of bias of the results of all outcomes included, except for all-cause mortality, was rated as high. This assessment deviates from that of the company, which rated the risk of bias as low for all outcomes included by the company (all-cause mortality, remission [PASI 100], health-related quality of life recorded with the DLQI (0 or 1) and SF-36, and outcomes on side effects).

The high risk of bias for health-related quality of life measured with the SF-36 resulted from the large proportion of patients imputed using MI (7% each for PCS and MCS in the guselkumab arm versus 42% for PCS and 41% for MCS in the fumaric acid ester arm).

The outcomes “remission” (PASI 100), “health-related quality of life” measured with the DLQI (0 or 1) and “SAEs” showed a high risk of bias due to potentially informative censoring.

The reason for the high risk of bias for specific AEs (infections and infestations, gastrointestinal disorders, and flushing) was the large proportion of patients with incomplete observation (at least 7% in the guselkumab arm versus 29% in the fumaric acid ester arm).

An additional reason for the high risk of bias for DLQI (0 or 1), SF-36, discontinuation due to AEs, infections and infestations, gastrointestinal disorders, and flushing was the lack of blinding in these subjectively recorded outcomes. The company described in Module 4 A that the outcome assessors in the study were blinded; however, according to the study documents, blinding was only mandated for PASI. Blinding to DLQI and SF-36, which are answered by patients, was not possible anyway due to the open-label study design.

No data were available for the outcomes “patient-reported symptoms” (PSSD) and “no psoriasis symptoms on the scalp” (ss-IGA 0). The risk of bias was therefore not assessed.

A detailed explanation on the risk of bias can be found in Section 2.6.2.4.3 of the full dossier assessment.

2.3.2.3 Results

Table 12, Table 13 and Table 14 summarize the results at or up to treatment week 24 on the comparison of guselkumab with fumaric acid esters in patients with moderate to severe plaque psoriasis who are not candidates for systemic treatment.

Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier. The table presents the outcomes “PASI 90” and “PASI 75” as supplementary information; the PASI 100 was primarily used for the derivation of the added benefit (see also Section 2.6.2.4.3 of the full dossier assessment). If available, Kaplan-Meier curves on the outcomes included are presented in Appendix A.1 of the full dossier assessment.

Table 12: Results (morbidity, health-related quality of life, side effects, time to event) – RCT: guselkumab vs. fumaric acid esters, week 24 (research question A)

Study Outcome category Outcome	Guselkumab N	Guselkumab Median time to event in days [95% CI] Patients with event n (%)	Fumaric acid esters N	Fumaric acid esters Median time to event in days [95% CI] Patients with event n (%)	Guselkumab vs. fumaric acid esters HR [95% CI]; p-value[a]
POLARIS					
Morbidity					
PASI					
Remission (PASI 100)	60	173.0 [170.0; NC] *20.1 (33.5)*[b]	59	NA *2.9 (4.9)*[b]	10.50 [2.48; 44.56]; 0.001
PASI 90	*60*	*112.0 [84.0; 113.0]* *52.6 (87.6)*[b]	*59*	*NA* *13.1 (22.2)*[b]	*7.47 [3.87; 14.41]; < 0.001*
PASI 75	*60*	*61.0 [57.0; 82.0]* *57.9 (96.6)*[b]	*59*	*140.0 [112.0; NC]* *27.3 (46.3)*[b]	*4.51 [2.80; 7.25]; < 0.001*
Patient-reported symptoms (PSSD)				No data	
No psoriasis symptoms on the scalp (ss-IGA 0)				No data	
Health-related quality of life					
DLQI (0 or 1)	60	133.0 [112.0; 168.0] 40.1 (66.9)[b]	59	173.0 [169.0; NC] 16.7 (28.2)[b]	3.29 [1.75; 6.16]; < 0.001
Side effects					
AEs (supplementary information)	60	28.0 [14.0; 56.0] 44 (73.3)	58	14.0 [9.0; 20.0] 57 (98.3)	–
SAEs	60	NA 3 (5.0)	58	NA 2 (3.4)	1.23 [0.21; 7.35]; 0.823

a: Effect, CI and p-value: Cox proportional hazards model.

b: No information was available on the number or on the proportion of patients with event up to week 24, which were included in the event time analysis. Hence an estimation of the numbers and proportions of the patients with event at week 24 is presented as additional information; the imputation of missing values was conducted using multiple imputation under unverifiable MAR assumption.

AE: adverse event; CI: confidence interval; DLQI: Dermatology Life Quality Index; HR: hazard ratio; MAR: missing at random; n: number of patients with one event; N: number of analysed patients; NA: not achieved; PSSD: Psoriasis Symptoms and Signs Diary; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; ss-IGA: Scalp-specific Investigator Global Assessment; vs.: versus

Table 13: Results (mortality, side effects, dichotomous) – RCT: guselkumab vs. fumaric acid esters, week 24 (research question A)

Study Outcome category Outcome	Guselkumab N	Guselkumab Patients with event n (%)	Fumaric acid esters N	Fumaric acid esters Patients with event n (%)	Guselkumab vs. fumaric acid esters RR [95% CI]; p-value[a]
POLARIS					
Mortality					
All-cause mortality	60	0 (0)	59	0 (0)	–
Side effects					
Discontinuation due to AEs	60	0 (0)	58	16 (27.6)	0.03 [0.00; 0.48][b]; < 0.001
Infections and infestations	60	30 (50.0)	58	25 (43.1)	1.16 [0.79; 1.71]; 0.467
Gastrointestinal disorders	60	13 (21.7)	58	47 (81.0)	0.27 [0.16; 0.44]; < 0.001[c]
Flushing	60	0 (0)	58	18 (31.0)	0.03 [0.00; 0.42]; < 0.001[d]

a: 2-sided asymptotic 95% CI, p-value calculated using the chi-square test according to Wald.
b: Effect estimation and CI calculated using an 0.5 continuity correction.
c: Institute‘s calculation of RR, CI (asymptotic) and p-value (unconditional exact test: CSZ method according to [5]).
d: Institute‘s calculation of RR, CI (asymptotic) using an 0.5 continuity correction, and p-value (unconditional exact test: CSZ method according to [5]).
AE: adverse event; CI: confidence interval; CSR: clinical study report; CSZ: convexity, symmetry, z score; n: number of patients with (at least) one event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 14: Results (health-related quality of life, continuous) – RCT, direct comparison: guselkumab vs. fumaric acid esters, week 24 (research question A)

Study Outcome category Outcome Scale	Guselkumab			Fumaric acid esters			Guselkumab vs. fumaric acid esters
	N[a]	Values at study start mean (SD)	Values at week 24 mean (SD)	N[a]	Values at study start mean (SD)	Values at week 24 mean (SD)	MD [95% CI]; p-value[b]
POLARIS							
Health-related quality of life							
SF-36							
PCS[c]	60	49.1 (7.2)	57.1 (5.3)	59	48.9 (7.4)	52.2 (6.7)	4.80 [2.09; 7.52]; < 0.001 SMD: 0.63 [0.26; 1.00][d]
Physical functioning					No data[e]		
Physical role functioning					No data[e]		
Bodily pain					No data[e]		
General health perception					No data[e]		
MCS[c]	60	44.8 (10.2)	50.8 (9.7)	59	40.1 (12.1)	48.6 (8.6)	−0.15 [−3.50; 3.21]; 0.931
Vitality					No data[e]		
Social functioning					No data[e]		
Emotional role functioning					No data[e]		
Mental wellbeing					No data[e]		

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Effect, CI and p-value: analysis of covariance (ANCOVA) of the changes from study start until study end with multiple imputation for the imputation of missing values. The ANCOVA model included the baseline values as covariables.
c: Higher values indicate improvement.
d: Institute's calculation of standardized mean difference and CI.
e: The company presented no analyses.
CI: confidence interval; MCS: Mental Component Summary; MD: mean difference; N: number of analysed patients; PCS: Physical Component Summary; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form (36) Health Survey; SMD: standardized mean difference; vs: versus

Only one study was available for the assessment. In addition, the risk of bias was rated as high for all outcomes except all-cause mortality (see Section 2.3.2.2). Consequently, at most hints, e.g. of an added benefit, can be derived for all outcomes, except for all-cause mortality. However, due to the size of the observed effects, it was not assumed that the effects for the

outcomes “remission” (PASI 100), “discontinuation due to AEs” and “flushing”, or the extent of the effects, were caused by systematic bias alone. Hence hereinafter, indications, e.g. of an added benefit, are derived for these outcomes.

Mortality

All-cause mortality

No deaths occurred in the POLARIS study up to week 24. There was no hint of an added benefit of guselkumab in comparison with fumaric acid esters; an added benefit is therefore not proven.

The company also described that no deaths occurred in the POLARIS study.

Morbidity

Remission (PASI 100)

For the outcome “remission”, recorded with the PASI 100, a statistically significant difference in favour of guselkumab was shown in comparison with fumaric acid esters. There was a high risk of bias for this outcome. Considering the size of the observed effect, however, it was not assumed that the effect and the extent of the effect were caused by systematic bias alone. Overall, this resulted in an indication of an added benefit of guselkumab in comparison with fumaric acid esters for the outcome “remission” (PASI 100).

This concurs with the assessment of the company, which derived an indication of an added benefit of guselkumab versus fumaric acid esters for the outcome “remission” (PASI 100).

Patient-reported symptoms (PSSD)

The company presented no data for the outcome “patient-reported symptoms” (PSSD). There was no hint of an added benefit of guselkumab in comparison with fumaric acid esters for patient-reported symptoms (PSSD); an added benefit is therefore not proven.

No psoriasis symptoms on the scalp (ss-IGA 0)

The company presented no data for the outcome “no psoriasis symptoms on the scalp” (ss-IGA 0). There was no hint of an added benefit of guselkumab in comparison with fumaric acid esters for the outcome “no psoriasis symptoms on the scalp” (ss-IGA 0); an added benefit is therefore not proven.

Health-related quality of life

DLQI (0 or 1)

A statistically significant difference in favour of guselkumab in comparison with fumaric acid esters was shown for the outcome “DLQI (0 or 1)”. Under consideration of the high risk of bias, there was a hint of an added benefit of guselkumab in comparison with fumaric acid esters.

This deviates from the assessment of the company, which derived an indication of an added benefit of guselkumab versus fumaric acid esters for the outcome “DLQI (0 or 1)”.

SF-36

The PCS and the MCS of the SF-36 were considered individually. The mean difference of the change from the start of the study until treatment week 24 was considered in each case.

The consideration of the mean differences showed no statistically significant difference between the treatment arms for the MCS. This resulted in no hint of an added benefit of guselkumab in comparison with fumaric acid esters; an added benefit for the outcome "MCS" is therefore not proven.

A statistically significant difference in favour of guselkumab in comparison with fumaric acid esters was shown for PCS, however. The CI for the SMD calculated by the Institute was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. Under consideration of the high risk of bias, there was a hint of an added benefit of guselkumab in comparison with fumaric acid esters for PCS.

This deviates from the assessment of the company, which presented both SF-36 summary scores (MCS and PCS), but did not consider them in the derivation of the added benefit of guselkumab versus fumaric acid esters.

Side effects

Serious adverse events

There was no statistically significant difference between the treatment arms for the outcome "SAEs". Hence for the outcome "SAEs", there was no hint of greater or lesser harm from guselkumab in comparison with fumaric acid esters; greater or lesser harm is therefore not proven.

This concurs with the assessment of the company, which derived no proof of an added benefit for the outcome "SAEs".

Discontinuation due to adverse events

A statistically significant result in favour of guselkumab in comparison with fumaric acid esters was shown for the outcome "discontinuation due to AEs". There was a high risk of bias also for this outcome. Considering the size of the observed effect, however, it was not assumed that the effect and the extent of the effect were caused by systematic bias alone. Overall, this resulted in an indication of lesser harm of guselkumab in comparison with fumaric acid esters for discontinuations due to AEs.

This concurs with the assessment of the company, which derived an indication of an added benefit of guselkumab versus fumaric acid esters for the outcome "discontinuation due to AEs".

Specific adverse events

Infections and infestations

No statistically significant difference between the treatment arms was shown for the outcome "infections and infestations". Hence for infections and infestations, there was no hint of greater or lesser harm from guselkumab in comparison with fumaric acid esters; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company, which presented the result for this outcome, but did not consider it in the derivation of the added benefit of guselkumab versus fumaric acid esters.

Gastrointestinal disorders

A statistically significant difference in favour of guselkumab for the outcome "gastrointestinal disorders" was shown between the treatment arms. Under consideration of the high risk of bias, there was a hint of lesser harm of guselkumab in comparison with fumaric acid esters for gastrointestinal disorders.

This deviates from the assessment of the company, which did not include this outcome in its assessment.

Flushing

A statistically significant difference in favour of guselkumab was shown for the outcome "flushing". There was a high risk of bias also for this outcome. Considering the size of the observed effect, however, it was not assumed that the effect and the extent of the effect were caused by systematic bias alone. Overall, this resulted in an indication of lesser harm of guselkumab in comparison with fumaric acid esters for the outcome "flushing".

This deviates from the assessment of the company, which did not include this outcome in its assessment.

2.3.2.4 Subgroups and other effect modifiers

The following subgroups were used for the present assessment:

- age (< 45 years/≥ 45 to < 65 years/≥ 65 years)
- sex (female/male)
- disease severity (PASI < 20/PASI ≥ 20)

All subgroup characteristics and cut-off values mentioned were prespecified. The company presented subgroup analyses for the following relevant outcomes: PASI 100, health-related quality of life measured with DLQI (0 or 1) and SF-36, SAEs and discontinuation due to AEs. There were no results on subgroup analyses for the further outcomes.

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

In accordance with the methods described above, no relevant effect modification was identified for the present research question. This concurs with the company's assessment.

2.3.3 Probability and extent of added benefit

The derivation of probability and extent of the added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

2.3.3.1 Assessment of added benefit at outcome level

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

Determination of the outcome category for outcomes on symptoms and side effects

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

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

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

The data recorded in the beginning of the study were used for assessing the severity of the symptoms. About 75% of the patients included had a PASI < 20. The median PASI score was about 15 (guselkumab) and 17 (adalimumab). Hence the PASI scores were rather in a non-serious range [6,7]. Based on this information, the outcome "remission" (PASI 100) was allocated to the category of non-serious/non-severe symptoms/late complications for the patients included in the study.

This allocation deviates from the assessment of the company, which allocated the outcome "PASI" to the category "serious/severe symptoms/late complications".

Determination of the outcome category for specific adverse events

The specific AEs "infections and infestations", "gastrointestinal disorders" and "flushing" were allocated to the outcome category "non-serious/non-severe side effects" because they occurred almost exclusively as non-SAEs.

The company did not consider these outcomes in the derivation on the added benefit and therefore did not allocate them to an outcome category.

Table 15: Extent of added benefit at outcome level: guselkumab vs. fumaric acid esters (research question A)

Outcome category **Outcome**	**Guselkumab vs. fumaric acid esters** **Median time to event or proportion of events or mean value at week 24** **Effect [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser benefit/added benefit not proven
Morbidity		
Remission (PASI 100)	Median: 173.0 days vs. NA HR: 10.50 [2.48; 44.56]; p = 0.001 HR: 0.10 [0.02; 0.40][c] probability: "indication"[d]	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Patient-reported symptoms (PSSD)	No data	Lesser benefit/added benefit not proven
No psoriasis symptoms on the scalp (ss-IGA 0)	No data	Lesser benefit/added benefit not proven
Health-related quality of life		
DLQI (0 or 1)	Median: 133.0 vs.173.0 days HR: 3.29 [1.75; 6.16]; p < 0.001 HR: 0.30 [0.16; 0.57][c] probability: "hint"	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5% added benefit, extent: "major"
SF-36		
PCS	Mean: 57.1 vs. 52.2 MD: 4.80 [2.09; 7.52]; p < 0.001 SMD: 0.63 [0.26; 1.00][e] probability: "hint"	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"
MCS	Mean: 50.8 vs. 48.6 MD: -0.15 [-3.50; 3.21]; p = 0.931	Lesser benefit/added benefit not proven

(continued)

Table 15: Extent of added benefit at outcome level: guselkumab vs. fumaric acid esters (research question A) (continued)

Outcome category **Outcome**	**Guselkumab vs. fumaric acid esters** **Median time to event or proportion of events or mean value at week 14** **Effect [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
Serious adverse events	NA vs. NA HR: 1.23 [0.21; 7.35]; p = 0.823	Greater/lesser harm not proven
Discontinuation due to adverse events	0% vs. 27.6% RR: 0.03 [0.00; 0.48]; p < 0.001 probability: "indication"[d]	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
Infections and infestations	50.0% vs. 43.1% RR: 1.16 [0.79; 1.71]; p = 0.467	Greater/lesser harm not proven
Gastrointestinal disorders	21.7% vs. 81.0% RR: 0.27 [0.16; 0.44]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
Flushing	0% vs. 31.0% RR: 0.03 [0.00; 0.42]; p < 0.001 probability: "indication"[d]	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d: The observed effect is so large that it cannot be explained solely by the impact of confounding factors.
e: If the CI of the SMD is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, it cannot be derived that a relevant effect is present.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; DLQI: Dermatology Life Quality Index; HR: hazard ratio; MCS: Mental Component Summary; MD: mean difference; PASI: Psoriasis Area and Severity Index; PCS: Physical Component Summary; PSSD: Psoriasis Symptoms and Signs Diary; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SMD: standardized mean difference; ss-IGA: Scalp-specific Investigator Global Assessment; vs.: versus

2.3.3.2 Overall conclusion on added benefit

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

Table 16: Positive and negative effects from the assessment of guselkumab in comparison with fumaric acid esters (research question A)

Positive effects	**Negative effects**
Morbidity ▪ Non-serious/non-severe symptoms/late complications ▫ remission (PASI 100): indication of an added benefit – extent: “considerable”	–
Health-related quality of life ▪ DLQI (0 or 1): hint of an added benefit – extent: “major” ▪ SF-36 (PCS): hint of an added benefit, extent: “non-quantifiable”	
Non-serious/non-severe side effects ▪ discontinuation due to AEs: indication of lesser harm – extent: “considerable” ▪ gastrointestinal disorders: hint of lesser harm – extent: “considerable” ▪ flushing: indication of lesser harm – extent: “considerable”	
Morbidity: ▪ PSSD: no data presented by the company ▪ no psoriasis symptoms on the scalp: no data presented by the company	
AE: adverse event; DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index; PCS: Physical Component Summary; PSSD: Psoriasis Symptoms and Signs Diary; SF-36: Short Form (36) Health Survey	

Overall, there were only positive effects of different certainty of results (indication or hint) for guselkumab in comparison with fumaric acid esters in the outcome categories of morbidity, health-related quality of life and side effects. The extent of the effects ranged from “considerable” to “major” or was “non-quantifiable”.

It must be taken into account in the overall consideration that the company’s dossier (including Module 5) presented no results for the assessment of patient-reported symptoms (PSSD) and no psoriasis symptoms on the scalp (ss-IGA 0), although these were recorded in the study and they were planned to be analysed.

In summary, there is an indication of considerable added benefit of guselkumab in comparison with fumaric acid esters for adult patients with moderate to severe plaque psoriasis who are candidates for systemic treatment. This concurs with the assessment of the company, which also derived an indication of considerable added benefit.

2.3.4 List of included studies

Janssen-Cilag. A study to compare the efficacy of guselkumab to fumaric acid esters for the treatment of participants with moderate to severe plaque psoriasis (POLARIS): full text view [online]. In: ClinicalTrials.gov. 06.09.2017 [Accessed: 18.12.2017]. URL: https://ClinicalTrials.gov/show/NCT02951533.

Janssen-Cilag. Multicenter, randomized, open-label, efficacy assessor-blinded, active comparator-controlled phase 3b study to compare the efficacy of guselkumab to fumaric acid esters (Fumaderm initial/ Fumaderm) for adult patients with moderate to severe plaque psoriasis who are candidates for and naive to systemic treatment [online]. In: EU Clinical Trials Register. [Accessed: 18.12.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-002135-15.

Janssen-Cilag. Multicenter, randomized, open-label, efficacy assessor-blinded, active comparator-controlled phase 3b study to compare the efficacy of guselkumab to fumaric acid esters (Fumaderm initial/ Fumaderm) for adult patients with moderate to severe plaque psoriasis who are candidates for and naive to systemic treatment (POLARIS): study CNTO1959PSO3008; clinical protocol [unpublished]. 2017.

Janssen-Cilag. Multicenter, randomized, open-label, efficacy assessor-blinded, active comparator-controlled phase 3b study to compare the efficacy of guselkumab to fumaric acid esters (Fumaderm initial/ Fumaderm) for adult patients with moderate to severe plaque psoriasis who are candidates for and naive to systemic treatment (POLARIS): study CNTO1959PSO3008; statistical analysis plan [unpublished]. 2017.

Janssen-Cilag. Multicenter, randomized, open-label, efficacy assessor-blinded, active comparator-controlled phase 3b study to compare the efficacy of guselkumab to fumaric acid esters (Fumaderm initial/Fumaderm) for adult patients with moderate to severe plaque psoriasis who are candidates for and naive to systemic treatment (POLARIS): study CNTO1959PSO3008; topline results report [unpublished]. 2017.

Janssen-Cilag. Multicenter, randomized, open-label, efficacy assessor-blinded, active comparator-controlled phase 3b study to compare the efficacy of guselkumab to fumaric acid esters (Fumaderm initial/ Fumaderm) for adult patients with moderate to severe plaque psoriasis who are candidates for and naive to systemic treatment (POLARIS): study CNTO1959PSO3008; Zusatzanalysen [unpublished]. 2017.

2.4 Research question B: adult patients with inadequate response to other systemic treatments or who are unsuitable for these treatments

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on guselkumab (status: 19 September 2017)
- bibliographical literature search on guselkumab (last search on 21 September 2017)
- search in trial registries for studies on guselkumab (last search on 19 September 2017)

To check the completeness of the study pool:

- search in trial registries for studies on guselkumab (last search on 4 December 2017)

Besides the studies VOYAGE 1 and VOYAGE 2 considered by the company, one additional potentially relevant study was identified from the check. This was the phase 2 study X-PLORE on the comparison of guselkumab with adalimumab [8], which the company excluded from the assessment due to the use of guselkumab, which was not in compliance with the SPC.

The company did not provide sufficient reasons for the exclusion of the study (see Section 2.6.2.3.2 of the full dossier assessment), but the exclusion had no consequence for the present benefit assessment for the following reason: The study arms of the X-PLORE study that were potentially relevant for the present research question (at most 26 patients in the guselkumab arm and 30 patients in the adalimumab arm) included fewer than 10% of the patients compared with the patient population of the meta-analysis of the studies VOYAGE 1 and VOYAGE 2 used for the benefit assessment.

2.4.1.1 Studies included

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

Table 17: Study pool – RCT, direct comparison: guselkumab vs. adalimumab (research question B)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
CNTO1959PSO3001 (VOYAGE 1[b])	Yes	Yes	No
CNTO1959PSO3002 (VOYAGE 2[b])	Yes	Yes	No

a: Study sponsored by the company.
b: In the following tables, the study is referred to with this abbreviated form.
RCT: randomized controlled trial; vs.: versus

Section 2.4.4 contains a reference list for the studies included.

2.4.1.2 Study characteristics

Table 18 and Table 19 describe the studies used for the benefit assessment.

Table 18: Characteristics of the studies included – RCT, direct comparison: guselkumab vs. adalimumab (research question B)

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	Guselkumab (N = 329) placebo[c] (N = 174) adalimumab (N = 334) Relevant subpopulation thereof: guselkumab (n = 150) adalimumab (n = 167)	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 12/2014–4/2016	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	Guselkumab (N = 496) placebo[c] (N = 248) adalimumab (N = 248) Relevant subpopulation thereof: guselkumab (n = 269) adalimumab (n = 132)	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 11/2014–5/2016	Primary: PASI 90, IGA score of 0 or 1 Secondary: all-cause mortality, symptoms, health-related quality of life, AEs

(continued)

Table 18: Characteristics of the studies included – RCT, direct comparison: guselkumab vs. adalimumab (research question B) (continued)

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for this benefit assessment.
b: Systemic treatment or phototherapy.
c: The arm is not relevant for the assessment and is not shown 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 19: Characteristics of the interventions – RCT, direct comparison: guselkumab vs. adalimumab (research question B)

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
- biological 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:

Concomitant treatment permitted:

- 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

(continued)

Table 19: Characteristics of the interventions – RCT, direct comparison: guselkumab vs. adalimumab (research question B) (continued)

Prior and concomitant treatment (VOYAGE 1, VOYAGE 2): **Concomitant treatment:** 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 biological 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

Description of the study design

The studies VOYAGE 1 and VOYAGE 2 were randomized, double-blind, parallel-group studies conducted in 101 and 115 study centres worldwide. The studies investigated guselkumab in comparison with placebo and adalimumab in adults with moderate to severe plaque psoriasis.

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 following study arms: guselkumab (VOYAGE 1: N = 329; VOYAGE 2: N = 496), placebo (VOYAGE 1: N = 174; VOYAGE 2: N = 248), and adalimumab (VOYAGE 1: N = 334; VOYAGE 2: N = 248). Randomization was stratified by study centres in both studies.

Both studies included patients who were candidates for either systemic therapy or phototherapy and who were either naive to systemic treatment or had already received systemic treatment. In both studies, the inclusion criteria were not restricted to patients of the present research question B, i.e. patients with inadequate response to systemic treatment (including ciclosporin, methotrexate and PUVA) or with intolerance or contraindication to such treatment. The company therefore presented the results of a subpopulation (see below).

Both studies defined disease severity using the following criteria: BSA ≥ 10%, PASI ≥ 12, and sPGA ≥ 3. The company further restricted its population for the benefit assessment by excluding patients with a DLQI ≤ 10 (see below).

Figure 1 and Figure 2 are schematic presentations of the study designs of the studies VOYAGE 1 and VOYAGE 2.

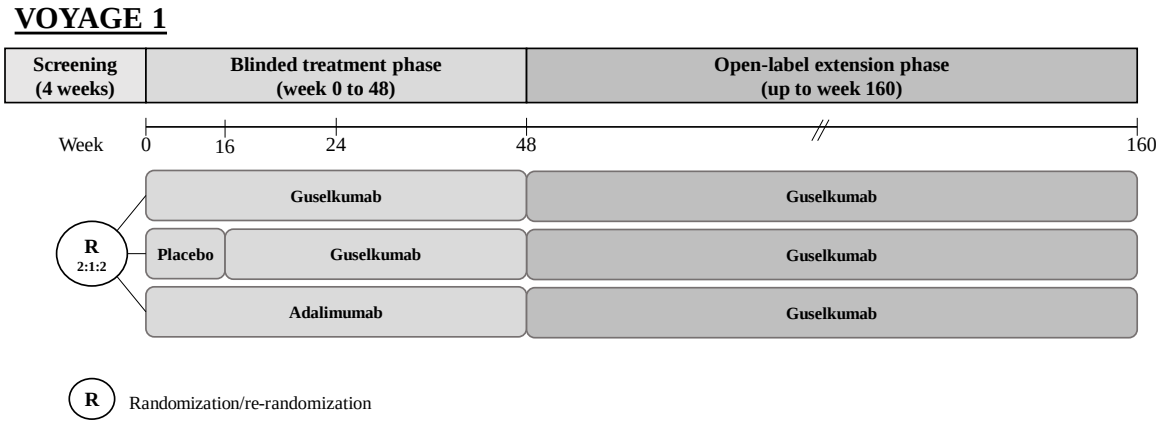
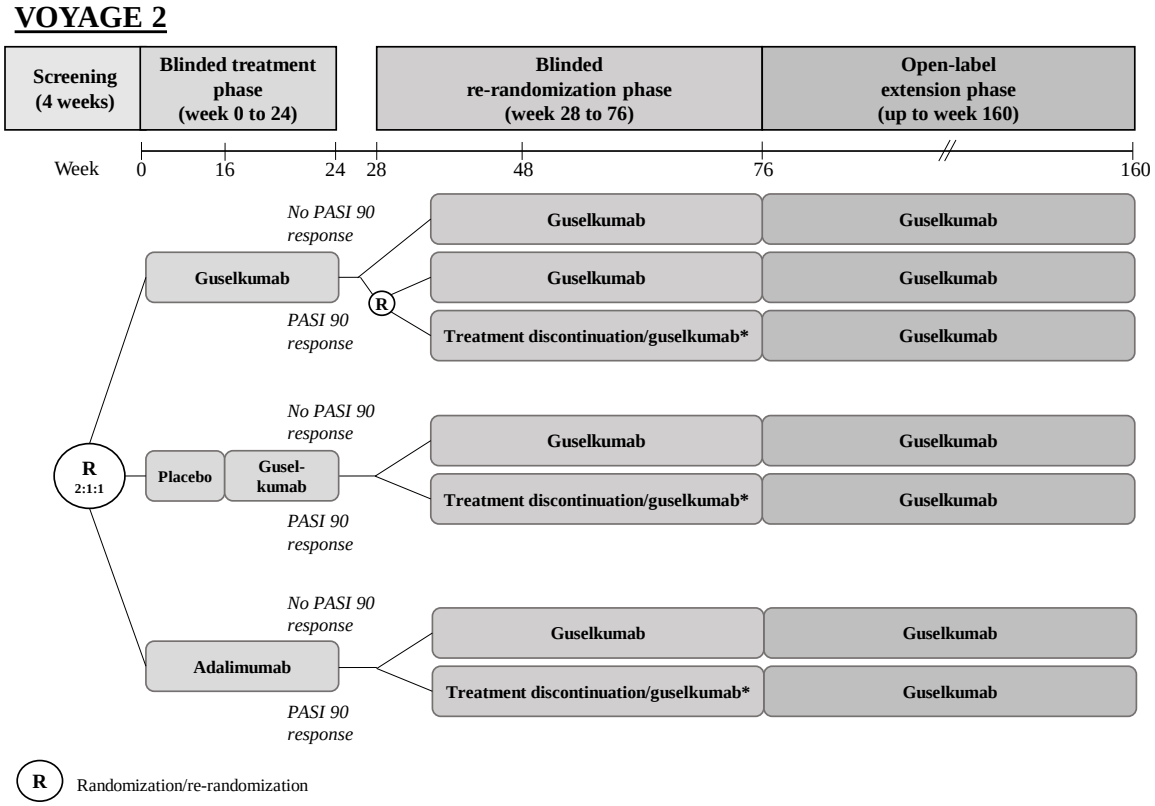


Figure 1: Schematic presentation of the VOYAGE 1 study design



* Randomized treatment discontinuation and (resumed) guselkumab treatment (on 50% loss of the achieved PASI improvement)

Figure 2: Schematic presentation of the VOYAGE 2 study design

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) and an open-label extension phase.

The course of the studies was identical until study week 28. In the VOYAGE 2 study, there was a re-randomization phase at week 28, based on the patients' individual PASI 90 response (week 28 to week 76). Patients of all treatment groups who had not achieved PASI 90 at week 28 received guselkumab from this time point. Patients from the guselkumab arm who had achieved PASI 90 were re-randomized in a 1:1 ratio to continued treatment with guselkumab or treatment discontinuation with resumed guselkumab treatment (on 50% loss of the achieved PASI improvement). Patients from the placebo and adalimumab arm with PASI 90 response discontinued treatment and received subsequent guselkumab treatment on 50% loss of the achieved PASI improvement.

The treatment or the re-randomization phase was followed by an open-label extension phase until week 160 both in the VOYAGE 1 and in the VOYAGE 2 study. In this extension phase, patients of all study arms were treated with guselkumab.

Both the re-randomization phase and the open-label extension phase were not relevant for the assessment because of the missing comparison with adalimumab and are therefore not considered further. The placebo arm was also not used for the assessment. This concurs with the company's approach.

Treatment in both studies, both in the guselkumab and in the adalimumab arm, was conducted according to the regimen described in Table 19 and was largely in compliance with the respective SPC [3,9]. According to the SPCs of guselkumab and adalimumab, consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Regarding this aspect, the study documents specified that consideration should be given to treatment discontinuation due to non-response up to week 28. In addition, the SPC of adalimumab specifies that, after 16 weeks, dosage frequency can be increased to 40 mg/week in patients with inadequate response; this dose adjustment was not considered in the studies. Both aspects were not addressed by the company in the dossier. It is assumed, however, that these deviations had no relevant influence on the study results.

Primary outcomes of both studies were PASI 90 and an 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.

Subpopulation relevant for the benefit assessment

Only subpopulations of the studies VOYAGE 1 and VOYAGE 2 were relevant for answering research question B, namely those patients for whom systemic drug treatment is inadequate or contraindicated or who do not tolerate such treatment. The company stated in Module 4 A that it had included the patient population described above in its assessment.

The captions of the additional analyses conducted for the company's dossier show that the company excluded those patients who had not received systemic treatment ("exclude treatment naive") for forming the subpopulation from the studies. It could not be inferred from the

information in the additional analyses whether the subpopulation formed by the company was composed of all pretreated patients who had already received systemic treatment and who, in accordance with the G-BA's definition of the subpopulation, also had discontinued their prior therapy for the reasons stated above. It is also possible that the subpopulation formed by the company was composed of all patients with prior systemic therapy, irrespective of the reason for their discontinuation of the prior therapy. The latter would be inadequate as, according to the study documents, the studies also included patients who had discontinued their prior systemic therapy for reasons other than inadequate response, contraindication or intolerance. If the company's subpopulation included patients who had switched treatment for other reasons, their proportion could be larger than 20%. The exact composition of the subpopulation formed by the company cannot be inferred from the patient characteristics presented by the company in the dossier. One of the reasons for this is that, at the same time, the company excluded patients with a DLQI ≤ 10 at the start of the study (see below). It therefore remains unclear overall whether the company implemented its intention to only include patients with inadequate response, contraindication or intolerance to systemic therapies.

As described above, the company additionally further restricted its population by excluding patients with a DLQI ≤ 10 from the study population of both studies. No uniform criteria exist for the definition of the severity of psoriasis. Both the criteria defined a priori in the VOYAGE studies and the company's criteria for the benefit assessment (under consideration of the DLQI) were a sufficient representation of moderate to severe plaque psoriasis. In addition, the company provided no explanation for excluding patients with a DLQI ≤ 10 from the study population. Hence the reasons for the company's unnecessary post hoc restriction of its subpopulation are overall unclear. The patients excluded by the company constituted about 30% of the total population of the studies (see also Section 2.6.2.4.1 of the full dossier assessment) with the proportion in relation to the subpopulation of interest being unclear.

Despite the described uncertainties, the subpopulation presented by the company was used as a sufficient approximation to the population relevant for research question B. The uncertainties were considered in the derivation of the certainty of conclusions of the results (see Section 2.4.2.2).

The subpopulation used for the assessment of research question B was about 45.6% (VOYAGE 1) and 54.2% (VOYAGE 2) of the patients randomized to the guselkumab arm, and 50.0% (VOYAGE 1) and 53.2% (VOYAGE 2) of the patients randomized to the adalimumab arm. It comprised n = 150 (VOYAGE 1) and n = 269 (VOYAGE 2) patients in the guselkumab arm, and n = 167 (VOYAGE 1) and n = 132 (VOYAGE 2) patients in the adalimumab arm.

Table 20 shows the characteristics of the patients in the studies included.

Table 20: Characteristics of the study populations – RCT, direct comparison: guselkumab vs. adalimumab (research question B)

Study Characteristics Category	**Guselkumab**	**Adalimumab**
VOYAGE 1	**N = 150**	**N = 167**
Age [years], mean (SD)	ND[a]	ND[a]
Sex [F/M], %	36.7/63.3	30.5/69.5
Ethnicity, n (%)		
White	107 (71.3)	127 (76.0)
Other[b]	43 (28.7)	40 (24.0)
Scalp involvement, n (%)	ND	ND
Face and neck involvement, n (%)	ND	ND
Hands and feet involvement, n (%)	ND	ND
Fingernail involvement, n (%)	ND	ND
Genital involvement, n (%)	ND	ND
Duration of disease [years], mean (SD)	ND[c]	ND[c]
PASI, mean (SD)	ND	ND
PASI ≥ 20, n (%)	76 (50.7)	94 (56.3)
DLQI, mean (SD)	ND	ND
IGA[d], n (%)		
0 to 3 (none to moderate)	115 (76.7)	114 (68.3)
4 (severe)	35 (23.3)	53 (31.7)
Psoriatic arthritis, n (%)	41 (27.3)	36 (21.6)
Pretreatment with, n (%)		
Phototherapy	109 (72.7)	102 (61.1)
Non-biological systemic treatment	141 (94.0)	151 (90.4)
Biologics	48 (32.0)	56 (33.5)
Treatment discontinuation, n (%)	ND[e]	ND[e]
Study discontinuation, n (%)	ND[e]	ND[e]
VOYAGE 2	N = 269	N = 132
Age [years], mean (SD)	ND[f]	ND[f]
Sex [F/M], %	29.4/70.6	33.3/66.7
Ethnicity, n (%)		
White	217 (80.7)	101 (76.5)
Other[b]	52 (19.3)	31 (23.5)
Scalp involvement, n (%)	ND	ND
Face and neck involvement, n (%)	ND	ND
Hands and feet involvement, n (%)	ND	ND
Fingernail involvement, n (%)	ND	ND
Genital involvement, n (%)	ND	ND
Duration of disease [years], mean (SD)	ND[g]	ND[g]

(continued)

Table 20: Characteristics of the study populations – RCT, direct comparison: guselkumab vs. adalimumab (research question B) (continued)

Study Characteristics Category	Guselkumab	Adalimumab
VOYAGE 2	**N = 269**	**N = 132**
PASI, mean (SD)	ND	ND
PASI ≥ 20, n (%)	142 (52.8)	69 (52.3)
DLQI, mean (SD)	ND	ND
IGA[d], n (%)		
0 to 3 (none to moderate)	206 (76.6)	103 (78.0)
4 (severe)	63 (23.4)	29 (22.0)
Psoriatic arthritis, n (%)	61 (22.7)	29 (22.0)
Pretreatment with, n (%)		
Phototherapy	192 (71.4)	87 (65.9)
Non-biological systemic treatment	250 (92.9)	116 (87.9)
Biologics	74 (27.5)	37 (28.0)
Treatment discontinuation, n (%)	ND[h]	ND[h]
Study discontinuation, n (%)	ND[h]	ND[h]

a: The company only presented categorial information on age [years]. Guselkumab: < 45: 52.7%; ≥ 45 to < 65: 41.3%; ≥ 65: 6.0%. Adalimumab: < 45: 54.5%; ≥ 45 to < 65: 42.5%; ≥ 65: 3.0%. The mean age in the total population was 43.9 years for guselkumab and 42.9 years for adalimumab.
b: Contains black, Asian, multiple origin, and other.
c: The company only presented categorial information on disease duration [years]. Guselkumab: < 15: 40.0%; ≥ 15; 60.0%. Adalimumab: < 15: 43.1%; ≥ 15; 56.9%. The mean disease duration in the total population was 17.9 years for guselkumab and 17.0 years for adalimumab.
d: IGA records the physician's assessment of the severity of the signs of redness, thickness and scaling. Categories 0 to 3 summarized by the company; information on individual categories is not available.
e: Up to week 48, 28 (8.5%) of the patients in the total population discontinued treatment with guselkumab and 52 (15.6%) discontinued treatment with adalimumab. Study participation was discontinued by 23 (7.0%) of the patients in the guselkumab arm and by 46 (13.8%) of the patients in the adalimumab arm.
f: The company only presented categorial information on age [years]. Guselkumab: < 45: 53.2%; ≥ 45 to < 65: 43.1%; ≥ 65: 3.7%. Adalimumab: < 45: 62.9%; ≥ 45 to < 65: 35.6%; ≥ 65: 1.5%. The mean age in the total population was 43.7 years for guselkumab and 43.2 years for adalimumab.
g: The company only presented categorial information on disease duration [years]. Guselkumab: < 15: 37.5%; ≥ 15; 62.5%. Adalimumab: < 15: 48.5%; ≥ 15; 51.5%. The mean disease duration in the total population was 17.9 years for guselkumab and 17.6 years for adalimumab.
h: Up to week 28, 26 (5.2%) of the patients in the total population discontinued treatment with guselkumab and 20 (8.1%) discontinued treatment with adalimumab. Information on the discontinuation of study participation until week 28 cannot be determined.

DLQI: Dermatology Life Quality Index; F: female; IGA: Investigator Global Assessment; M: male, n: number of patients in the category; N: number of randomized patients; ND: no data; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The demographic and clinical characteristics of the patients in these subpopulations were largely balanced both between the individual study arms and between the studies.

In both study, most participants were younger than 45 years, male and white. The PASI score at the start of the study was mostly 20 or higher.

The company provided no information on treatment and study discontinuation for the relevant subpopulations of the studies. Based on the available information for the total population, it is not assumed that there was a relevant proportion of patients who discontinued treatment or the study in the subpopulation.

Table 21 shows the risk of bias at study level.

Table 21: Risk of bias at study level – RCT, direct comparison: guselkumab vs. adalimumab esters (research question B)

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

The risk of bias at study level was classed as low for both studies. This concurs with the company's assessment.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - remission (PASI 100)
  - patient-reported symptoms (PSSD)
  - no psoriasis symptoms on the scalp (ss-IGA 0)
  - no psoriasis symptoms on the hands and feet (hf-PGA 0)
  - no psoriasis symptoms on the nails (NAPSI 0)

- Health-related quality of life
  - DLQI (0 or 1)
  - SF-36
- Side effects
  - SAEs
  - discontinuation due to AEs
  - infections and infestations
  - if applicable, further specific AEs

Whereas results at week 24 and week 48 were available for the VOYAGE 1 study, only the results at week 24 were relevant for the VOYAGE 2 study. Consideration of the longer observation period would principally be preferable for the present benefit assessment. Meta-analysis of the results at week 48 of the VOYAGE 1 study with those at week 24 of the VOYAGE 2 study appears to be inadequate due to the notable difference in observation periods, however. It was therefore checked for the benefit assessment whether there were differences in the effects of both time points of analysis in the VOYAGE 1 study. Since no important deviations were shown between the 24-week analyses and the 48-week analyses for almost all outcomes, a meta-analysis of the results at week 24 (or at week 28 for side effects) is possible in the present situation without relevant loss of information (see Section 2.6.2.4.3 of the full dossier assessment). The results of the VOYAGE 1 study at week 48 are presented in Appendix C of the full dossier assessment as supplementary information.

The choice of patient-relevant outcomes deviated from that of the company, which, on the one hand, did not include the outcomes “no psoriasis symptoms on the scalp” and “no psoriasis symptoms on the hands and feet” in the dossier (Module 4 A), and, on the other, used further outcomes (see Section 2.6.2.4.3 of the full dossier assessment).

The company presented different analyses for the outcomes it used. In the present benefit assessment, both analyses on the proportion of patients with event at week 24 and analyses on the time to first event were used for PASI 100, PSSD (Sign score 0 and Symptom score 0), NAPSI 0 and DLQI (0 or 1). Analyses on the mean change from the mixed-effects model repeated measures (MMRM) were used for health-related quality of life measured with the SF-36. Analyses using the proportion of patients with event up to week 24 were used for the outcomes of all-cause mortality, SAEs, discontinuation due to AEs, and infections and infestations (see also Section 2.6.2.4.3 of the full dossier assessment).

Table 22 shows for which outcomes data were available in the studies included.

Table 22: Matrix of outcomes – RCT, direct comparison: guselkumab vs. adalimumab (research question B)

Study	Outcomes											
	All-cause mortality	Remission (PASI 100)[a, b]	Patient-reported symptoms (PSSD)[b]	No psoriasis symptoms on the scalp (ss-IGA 0)[b]	No psoriasis symptoms on the nails (NAPSI 0)[b]	No psoriasis symptoms on hands and feet (hf-PGA 0)[b]	Health-related quality of life (DLQI 0 or 1)[b]	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Infections and infestations[c]	If applicable, further specific AEs
VOYAGE 1 (24/28[d] weeks)	Yes	Yes	Yes	No[e]	Yes	No[e]	Yes	No[f]	Yes	Yes	Yes	No[g]
VOYAGE 2 (24/28[d] weeks)	Yes	Yes	Yes	No[e]	Yes	No[e]	Yes	Yes	Yes	Yes	Yes	No[g]

a: Improvement in score by 100% compared with the start of the study.
b: Analysis using the proportion of patients with event at week 24 and using the time to first event were used for this outcome.
c: The company's operationalization in Module 4 A of the dossier is unclear (see Section 2.6.2.4.3 of the full dossier assessment).
d: The outcomes on the category of side effects were observed until week 28.
e: The company did not include the outcome in its assessment and presented no analyses for the relevant subpopulation (see Section 2.6.2.4.3 of the full dossier assessment).
f: Outcome not recorded.
g: No conclusive choice of specific AEs for the relevant subpopulation is possible based on the documents presented by the company (see Section 2.6.2.4.3 of the full dossier assessment).

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

2.4.2.2 Risk of bias

Table 23 describes the risk of bias for the relevant outcomes.

Table 23: Risk of bias at study and outcome level – RCT, direct comparison: guselkumab vs. adalimumab (research question B)

Study Time point	Outcomes												
	Study level	All-cause mortality	Remission (PASI 100)[a, b]	Patient-reported symptoms (PSSD)[b]	No psoriasis symptoms on the scalp (ss-IGA 0)[c]	No psoriasis symptoms on the nails (NAPSI 0)[b, c]	No psoriasis symptoms on hands and feet (hf-PGA 0)[c]	Health-related quality of life (DLQI 0 or 1)[b]	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Infections and infestations[d]	If applicable, further specific AEs
VOYAGE 1 24/28[e] weeks	L	L	L	H[f]	–[g]	H[h]	–[g]	L	–[i]	L	L	L	–[j]
VOYAGE 2 24/28[e] weeks	L	L	L	H[f]	–[g]	H[h]	–[g]	L	L	L	L	L	–[j]

a: Improvement in score by 100% compared with the start of the study.
b: Analysis using the proportion of patients with event at week 24 and using the time to first event were used for this outcome, and the risk of bias of the results was assessed in each case.
c: The analysis only comprises patients with NAPSI > 0, ss-IGA > 0 or hf-PGA > 0 at the start of the study.
d: The company's operationalization in Module 4 A of the dossier is unclear for the relevant subpopulation (see Section 2.6.2.4.3 of the full dossier assessment).
e: The outcomes on the category of side effects were observed until week 28.
f: Proportion of patients with event: large proportion (> 15%) or large difference between the treatment groups (VOYAGE 2: > 10 percentage points) regarding imputed values; time to first event: possibly large proportion of potentially informative censorings.
g: The company did not include the outcome in its assessment and presented no analyses for the relevant subpopulation (see Section 2.6.2.4.3 of the full dossier assessment).
h: Proportion of patients with event: proportion of imputed values unknown; time to first event: possibly large proportion of potentially informative censorings.
i: Outcome not recorded.
j: No conclusive choice of specific AEs for the relevant subpopulation is possible based on the documents presented by the company (see Section 2.6.2.4.3 of the full dossier assessment).

AE: adverse event; DLQI: Dermatology Life Quality Index; H: high; hf-PGA: Physician Global Assessment of Hands and/or Feet; L: low; 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

The risk of bias of the results of all outcomes was rated as low, except for patient-reported symptoms (PSSD) and no psoriasis symptoms on the nails (NAPSI 0). This deviates from the assessment of the company insofar as the company assessed the risk of bias as low for all outcomes, including PSSD and NAPSI 0.

For the analyses of the PSSD using the proportion of patients with event, the high risk of bias resulted from the large proportion of imputed values (> 15%) and the large difference in imputed values between the treatment groups (VOYAGE 2: > 10 percentage points). The proportion of imputed values was unknown for the proportion of patients with NAPSI 0, which is why there is a high risk of bias also here. There was a high risk of bias, which was caused by the possible large proportion of potentially informative censorings, also for the analyses of NAPSI 0 and PSSD using the time to event. Detailed comments on the risk of bias can be found in Section 2.6.2.4.2 of the full dossier assessment.

No data for the outcomes “no psoriasis symptoms on the scalp” (ss-IGA 0) and “no psoriasis symptoms on hands and feet” (hf-PGA 0) were available for the relevant subpopulation. In addition, a choice of further specific AEs based on the documents presented by the company was not possible (see Section 2.6.2.4.3 of the full dossier assessment). Hence the risk of bias was not assessed for these outcomes.

Overall assessment of the certainty of conclusions

It is unclear for the present benefit assessment whether, in compliance with the requirement of the G-BA, the company only included patients with inadequate response to prior systemic treatment or with intolerance or contraindication to such treatment when forming its subpopulation.

In addition, the company excluded all patients with DLQI ≤ 10 at the start of the study (see Section 2.4.1.2 and Section 2.6.2.4.1 of the full dossier assessment). The influence on the size of the relevant subpopulation is unclear. In the total population of both studies, about 30% of the patients had a DLQI ≤ 10 at the start of the study.

As a result of these 2 uncertainties, at most indications, e.g. of an added benefit, could be derived from the meta-analysis of the studies VOYAGE 1 and VOYAGE 2 for all outcomes presented.

For the outcomes “PSSD” and NAPSI 0”, there was an additional high risk of bias in the analyses using the proportion of patients with event due to the high or unknown proportion of imputed values. In the presence of a statistically significant effect, this benefit assessment addresses this problem with sensitivity analyses conducted by the Institute (see Section 2.6.2.2 of the full dossier assessment). If the result is robust after the check with sensitivity analyses conducted by the Institute, this does not lead to further downgrading of the certainty of conclusions; in case of a non-robust result, at most a hint, e.g. of an added benefit, can be derived for the outcomes “PSSD” and NAPSI 0”.

2.4.2.3 Results

Table 24 to Table 29 summarize the results at treatment week 24 or 28 for AE outcomes on the comparison of guselkumab versus adalimumab in patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments or who are not candidates for such treatments. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The outcomes "PASI 90" and "PASI 75" are presented as supplementary information; PASI 100 was primarily used for the derivation of the added benefit (see also Section 2.6.2.4.3 of the full dossier assessment).

If available, Kaplan-Meier curves on the outcomes included are presented in Appendix B.1 of the full dossier assessment. The forest plots on the sensitivity analyses conducted by the Institute can be found in Appendix B.2 of the full dossier assessment.

Table 24: Results (mortality, morbidity, health-related quality of life, dichotomous) – RCT, direct comparison: guselkumab vs. adalimumab, week 24 (research question B)

Outcome category **Outcome**	**Guselkumab**		**Adalimumab**		**Guselkumab vs. adalimumab**
Study	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
Mortality					
All-cause mortality					
VOYAGE 1	150	0 (0)	166	0 (0)	–
VOYAGE 2	269	0 (0)	132	0 (0)	–
Morbidity					
PASI[b]					
Remission (PASI 100)					
VOYAGE 1	150	60 (40.0)[c]	167	45 (26.9)[c]	1.49 [1.08; 2.05]; 0.013
VOYAGE 2	269	118 (43.9)[d]	132	32 (24.2)[d]	1.73 [1.24; 2.40]; < 0.001
Total					1.60 [1.27; 2.02]; < 0.01[e]
PASI 90[b]					
VOYAGE 1	*150*	*114 (76.0)[c]*	*167*	*89 (53.3)[c]*	*1.39 [1.18; 1.64]; < 0.001*
VOYAGE 2	*269*	*208 (77.3)[d]*	*132*	*76 (57.6)[d]*	*1.34 [1.14; 1.57]; < 0.001*
Total					*1.36 [1.22; 1.53]; < 0.01[e]*
PASI 75[b]					
VOYAGE 1	*150*	*137 (91.3)[c]*	*167*	*118 (70.7)[c]*	*1.26 [1.13; 1.40]; < 0.001*
VOYAGE 2	*269*	*247 (91.8)[d]*	*132*	*95 (72.0)[d]*	*1.26 [1.13; 1.41]; < 0.001*
Total					*1.26 [1.17; 1.36]; < 0.01[e]*

(continued)

Table 24: Results (mortality, morbidity, health-related quality of life, dichotomous) – RCT, direct comparison: guselkumab vs. adalimumab, week 24 (research question B) (continued)

Outcome category Outcome Study	Guselkumab N	Guselkumab Patients with event n (%)	Adalimumab N	Adalimumab Patients with event n (%)	Guselkumab vs. adalimumab RR [95% CI]; p-value[a]
Morbidity					
Patient-reported symptoms (PSSD)					
Symptom score 0[b]					
VOYAGE 1	150	44 (29.3)[f]	167	26 (15.6)[f]	1.86 [1.20; 2.89]; 0.004
VOYAGE 2	269	74 (27.5)[g]	132	17 (12.9)[g]	1.99 [1.25; 3.17]; 0.002
Total					1.92 [1.40; 2.64]; < 0.01[e]
Sensitivity analysis[h]					
VOYAGE 1					1.55 [1.02; 2.37]; NC
VOYAGE 2					1.72 [1.07; 2.76]; NC
Total					1.62 [1.18; 2.22]; 0.003[i]
Sign score 0[b]					
VOYAGE 1	150	35 (23.3)[f]	167	16 (9.6)[f]	2.30 [1.34; 3.95]; 0.002
VOYAGE 2	269	63 (23.4)[g]	132	13 (9.8)[g]	2.17 [1.29; 3.65]; 0.002
Total					2.23 [1.53; 3.25]; < 0.01[e]
Sensitivity analysis[h]					
VOYAGE 1					1.95 [1.13; 3.37]; NC
VOYAGE 2					1.90 [1.09; 3.29]; NC
Total					1.92 [1.30; 2.84]; < 0.001[i]
No psoriasis symptoms on the scalp (ss-IGA 0)					
VOYAGE 1	No results available for the relevant subpopulation[j]				
VOYAGE 2	No results available for the relevant subpopulation[j]				
No psoriasis symptoms on hands and feet (hf-PGA 0)					
VOYAGE 1	No results available for the relevant subpopulation[j]				
VOYAGE 2	No results available for the relevant subpopulation[j]				
Health-related quality of life					
DLQI (0 or 1)[b]					
VOYAGE 1	150	82 (54.7)[k]	167	58 (34.7)[k]	1.63 [1.27; 2.09]; < 0.001
VOYAGE 2	269	139 (51.7)[l]	132	43 (32.6)[l]	1.56 [1.19; 2.07]; < 0.001
Total					1.60 [1.33; 1.92]; < 0.01[e]

(continued)

Table 24: Results (mortality, morbidity, health-related quality of life, dichotomous) – RCT, direct comparison: guselkumab vs. adalimumab, week 24 (research question B) (continued)

a: RR, 95% CI and p-value were determined with the Cochran-Mantel-Haenszel method under consideration of the stratification according to study centres.
b: NRI analysis.
c: There is no information on the number of imputed values for the relevant subpopulation. It can be inferred from the information provided in the CSR on the total population that, at week 24, 4.3% of the values in the guselkumab arm and 3.9% of the values in the adalimumab arm were imputed as non-response in the corresponding analysis.
d: There is no information on the number of imputed values for the relevant subpopulation. It can be inferred from the information provided in the CSR on the total population that, at week 24, 4.8% of the values in the guselkumab arm and 4.4% of the values in the adalimumab arm were imputed as non-response in the corresponding analysis.
e: Meta-analysis with fixed effect (inverse variance method).
f: There is no information on the number of imputed values. It is known, however, that there was no recording for 17.3% and 26.9% of the patients (guselkumab and adalimumab) of the relevant subpopulation at week 24.
g: There is no information on the number of imputed values. It is known, however, that there was no recording for 14.9% and 26.5% of the patients (guselkumab and adalimumab) of the relevant subpopulation at week 24.
h: Due to the large proportion of imputed values, the Institute conducted a sensitivity analysis. Missing values were imputed in accordance with the response rate observed in the control group. The information on the return was used for the proportions of missing values. A correction of variance was conducted according to the data-set re-sizing approach (approach W3 in [10]).
i: Institute's calculation. Meta-analysis with fixed effect (inverse variance method).
j: The company presented no analyses for the relevant subpopulation.
k: There is no information on the number of imputed values. It is known, however, that there was no recording for 4.7% and 6.0% of the patients (guselkumab and adalimumab) of the relevant subpopulation at week 24.
l: There is no information on the number of imputed values. It is known, however, that there was no recording for 3.3% and 7.6% of the patients (guselkumab and adalimumab) of the relevant subpopulation at week 24.

CI: confidence interval; DLQI: Dermatology Life Quality Index; hf-PGA: Physician Global Assessment of Hands and/or Feet; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculated; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PSSD: Psoriasis Symptoms and Signs Diary; RCT: randomized controlled trial; RR: relative risk; ss-IGA: Scalp-specific Investigator Global Assessment; vs.: versus

Table 25: Results (morbidity, health-related quality of life, time to event) – RCT, direct comparison: guselkumab vs. adalimumab, week 24 (research question B)

Outcome category Outcome Study	Guselkumab N	Guselkumab Median time to event in months [95% CI] Patients with event n (%)	Adalimumab N	Adalimumab Median time to event in months [95% CI] Patients with event n (%)	Guselkumab vs. adalimumab HR [95% CI]; p-value[a]
Morbidity					
PASI					
Remission (PASI 100)					
VOYAGE 1	150	NA [4.63; NC] ND	167	NA ND	1.67 [1.16; 2.41]; 0.006
VOYAGE 2	269	NA [4.67; NC] ND	132	NA ND	1.84 [1.27; 2.68]; 0.001
Total					1.75 [1.35; 2.27]; < 0.01[b]
PASI 90					
VOYAGE 1	*150*	*2.79 [2.79; 3.22]* *ND*	*167*	*3.68 [2.83; 3.75]* *ND*	*1.48 [1.12; 1.95]; 0.005*
VOYAGE 2	*269*	*2.79 [2.76; 2.83]* *ND*	*132*	*3.71 [2.92; 4.63]* *ND*	*1.72 [1.31; 2.26]; < 0.001*
Total					*1.60 [1.32; 1.94]; < 0.01[b]*
PASI 75					
VOYAGE 1	*150*	*1.91 [1.87; 1.94]* *ND*	*167*	*1.87 [1.87; 2.10]* *ND*	*1.15 [0.89; 1.48]; 0.294*
VOYAGE 2	*269*	*1.87 [1.87; 1.91]* *ND*	*132*	*1.96 [1.87; 2.79]* *ND*	*1.23 [0.96; 1.58]; 0.098*
Total					*1.19 [1.00; 1.42]; 0.06[b]*
Patient-reported symptoms (PSSD)					
Symptom score 0					
VOYAGE 1	150	NA ND	167	NA ND	1.78 [1.16; 2.72]; 0.008
VOYAGE 2	269	NA ND	132	NA ND	1.98 [1.28; 3.07]; 0.002
Total					1.87 [1.38; 2.54]; < 0.01[b]
Sign score 0					
VOYAGE 1	150	NA ND	167	NA ND	1.69 [1.05; 2.72]; 0.032
VOYAGE 2	269	NA ND	132	NA ND	2.05 [1.26; 3.32]; 0.004
Total					1.86 [1.32; 2.61]; < 0.01[b]

(continued)

Table 25: Results (morbidity, health-related quality of life, time to event) – RCT, direct comparison: guselkumab vs. adalimumab, week 24 (research question B) (continued)

Outcome category Outcome Study	Guselkumab N	Guselkumab Median time to event in months [95% CI] Patients with event n (%)	Adalimumab N	Adalimumab Median time to event in months [95% CI] Patients with event n (%)	Guselkumab vs. adalimumab HR [95% CI]; p-value[a]
Morbidity					
No psoriasis symptoms on the scalp (ss-IGA 0)	No results available for the relevant subpopulation[c]				
No psoriasis symptoms on hands and feet (hf-PGA 0)	No results available for the relevant subpopulation[c]				
Health-related quality of life					
DLQI (0 or 1)					
VOYAGE 1	150	5.52 [3.75; NC] ND	167	NA ND	1.71 [1.20; 2.43]; 0.003
VOYAGE 2	269	5.49 [3.78; NC] ND	132	NA ND	1.49 [1.06; 2.10]; 0.021
Total					1.59 [1.25; 2.04]; < 0.01[b]

a: HR, CI and p-value: Cox proportional hazards model, stratified by study centres.
b: Meta-analysis with fixed effect (inverse variance method).
c: The company presented no analyses for the relevant subpopulation.

CI: confidence interval; DLQI: Dermatology Life Quality Index; hf-PGA: Physician Global Assessment of Hands and/or Feet; HR: hazard ratio; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PSSD: Psoriasis Symptoms and Signs Diary; RCT: randomized controlled trial; ss-IGA: Scalp-specific Investigator Global Assessment; vs.: versus

Table 26: Results for patients with nail psoriasis at study start (morbidity [NAPSI], dichotomous) – RCT, direct comparison: guselkumab vs. adalimumab, week 24 (research question B)

Outcome category Outcome Study	Guselkumab N[a]	 Patients with event n (%)	Adalimumab N[a]	 Patients with event n (%)	Guselkumab vs. adalimumab RR [95% CI]; p-value[b]
Morbidity					
No psoriasis symptoms on the nails					
NAPSI 0[c]					
VOYAGE 1	97	20 (20.6)	105	31 (29.5)	0.70 [0.43; 1.14]; NC
VOYAGE 2	166	60 (36.1)	77	23 (29.9)	1.21 [0.81; 1.80]; NC
Total					0.97 [0.71; 1.32]; 0.861[d]

a: According to the CSR, the outcome was only recorded during the study in patients with nail psoriasis at the start of the study. The company provided no explicit information on the number of patients in the relevant subpopulation who were affected at the start of the study. Due to the analyses for the operationalization using the change since start of the study that were also presented, it is assumed that this applied to the numbers provided.
b: Institute's calculation of RR and CI (asymptotic).
c: NRI analysis; proportion of imputed values is unknown.
d: Institute's calculation. Meta-analysis with fixed effect (inverse variance method).

CI: confidence interval; n: number of patients with event; CSR: clinical study report; N: number of analysed patients; NAPSI: Nail Psoriasis Severity Index; NC: not calculated; NRI: non-responder imputation; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 27: Results for patients with nail psoriasis at study start (morbidity [NAPSI], time to event) – RCT, direct comparison: guselkumab vs. adalimumab, week 24 (research question B)

Outcome category Outcome Study	Guselkumab N[a]	Guselkumab Median time to event in months [95% CI] Patients with event n (%)	Adalimumab N[a]	Adalimumab Median time to event in months [95% CI] Patients with event n (%)	Guselkumab vs. adalimumab HR [95% CI]; p-value[b]
Morbidity					
No psoriasis symptoms on the nails					
NAPSI 0					
VOYAGE 1	150	NA [ND] ND	167	NA [ND] ND	0.53 [0.29; 1.00]; 0.050
VOYAGE 2	269	NA [ND] ND	132	NA [ND] ND	1.18 [0.71; 1.96]; 0.530
Total					0.86 [0.58; 1.27]; 0.43[c]

a: According to the CSR, the outcome was only recorded during the study in patients with nail psoriasis at the start of the study. The company provided no explicit information on the number of patients in the relevant subpopulation who were affected at the start of the study. Due to the analyses for the operationalization using the change since start of the study that were also presented, it is assumed that this applied to about 60% of the patients. The company did not describe how the remaining 40% of the patients were dealt with in the available analysis.
b: HR, 95% CI and p-value: Cox proportional hazards model, stratified by study centres.
c: Meta-analysis with fixed effect (inverse variance method).

CI: confidence interval; CSR: clinical study report; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NAPSI: Nail Psoriasis Severity Index; ND: no data; RCT: randomized controlled trial; vs.: versus

Table 28: Results (health-related quality of life, continuous) – RCT, direct comparison: guselkumab vs. adalimumab, week 24 (research question B)

Study Outcome category Outcome Scale	Guselkumab N[a]	Guselkumab Values at study start mean (SD)	Guselkumab Values at week 24 mean (SD)	Adalimumab N[a]	Adalimumab Values at study start mean (SD)	Adalimumab Values at week 24 mean (SD)	Guselkumab vs. adalimumab MD [95% CI]; p-value[b]
VOYAGE 2							
Health-related quality of life							
SF-36							
PCS[c]	260	45.13 (9.13)	52.81 (7.74)	120	46.21 (8.93)	51.37 (8.36)	2.2 [0.8; 3.6]; 0.002 SMD: 0.33 [0.1; 0.6]
Physical functioning	260	46.71 (9.71)	52.70 (7.31)	120	47.88 (9.65)	51.56 (8.36)	2.0 [0.7; 3.4]
Physical role functioning	260	43.70 (9.94)	51.22 (7.10)	120	43.68 (9.75)	49.40 (8.15)	2.0 [0.6; 3.5]
Bodily pain	260	40.86 (10.06)	53.08 (9.16)	120	42.81 (11.08)	50.99 (10.63)	2.9 [0.9; 4.8]
General health perception	260	43.39 (9.98)	49.69 (9.30)	120	42.83 (9.53)	46.97 (9.48)	2.4 [0.8; 4.0]
MCS[c]	260	41.57 (11.68)	49.27 (9.04)	120	40.64 (10.68)	46.08 (10.23)	2.6 [0.9; 4.3]; 0.003 SMD: 0.31 [0.1; 0.5]
Vitality	260	45.88 (9.32)	52.93 (8.84)	120	45.59 (10.01)	50.49 (9.69)	2.1 [0.4; 3.8]
Social functioning	260	40.51 (11.27)	50.78 (8.06)	120	39.92 (10.05)	47.19 (9.76)	3.4 [1.6; 5.1]
Emotional role functioning	260	42.71 (12.01)	49.81 (8.31)	120	42.33 (10.73)	47.80 (9.49)	1.9 [0.2; 3.6]
Mental wellbeing	260	41.21 (10.81)	49.01 (8.62)	120	41.01 (10.54)	45.92 (9.69)	2.9 [1.2; 4.7]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Effect, CI and p-value: MMRM analysis of the changes from start of study to end of study.
c: Higher values indicate improvement.

CI: confidence interval; MCS: Mental Component Summary; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; PCS: Physical Component Summary; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form (36) Health Survey; SMD: standardized mean difference; vs: versus

Table 29: Results (side effects, dichotomous) – RCT, direct comparison: guselkumab vs. adalimumab, week 28 (research question B)

Outcome category Outcome Study	Guselkumab N	Guselkumab Patients with event n (%)	Adalimumab N	Adalimumab Patients with event n (%)	Guselkumab vs. adalimumab RR [95% CI]; p-value[a]
Side effects					
AEs (supplementary information)					
VOYAGE 1	150	97 (64.7)	166	110 (66.3)	–
VOYAGE 2	269	155 (57.6)	132	80 (60.6)	–
SAEs					
VOYAGE 1	150	3 (2.0)	166	7 (4.2)	0.47 [0.13; 1.80]; 0.342
VOYAGE 2	269	9 (3.3)	132	6 (4.5)	0.74 [0.27; 2.03]; 0.581
Total					0.63 [0.28; 1.40]; 0.26[b]
Discontinuation due to AEs					
VOYAGE 1	150	2 (1.3)	166	6 (3.6)	0.37 [0.08; 1.80]; 0.288
VOYAGE 2	269	4 (1.5)	132	4 (3.0)	0.49 [0.13; 1.93]; 0.448
Total					0.43 [0.15; 1.22]; 0.11[b]
Infections and infestations					
VOYAGE 1	150	51 (34.0)	166	61 (36.7)	0.93 [0.69; 1.25]; 0.639
VOYAGE 2	269	91 (33.8)	132	42 (31.8)	1.06 [0.79; 1.44]; 0.736
Total					0.99 [0.80; 1.23]; 0.94[b]
If applicable, further specific AEs				ND[c]	

a: RR, 95% CI and p-value were determined with the Cochran-Mantel-Haenszel method under consideration of the stratification according to study centres.
b: Meta-analysis with fixed effect (inverse variance method).
c: No conclusive choice of specific AEs for the relevant subpopulation is possible based on the documents presented by the company (see Section 2.6.2.4.3 of the full dossier assessment).
AE: adverse event; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

As shown in Section 2.4.2.2, the certainty of conclusions of the results on the basis of the available data was reduced. Hence, at most indications, e.g. of an added benefit, can be determined. This deviates from the approach of the company, which derived proof.

Mortality

All-cause mortality

No deaths occurred in the studies VOYAGE 1 and VOYAGE 2 until treatment week 24. There was no hint of an added benefit of guselkumab in comparison with adalimumab for all-cause mortality; an added benefit is therefore not proven.

The company also described that no deaths occurred in both VOYAGE studies until week 24.

Morbidity

Remission (PASI 100)

Regarding the outcome "remission", determined with PASI 100, the meta-analysis of the studies showed a statistically significant effect in favour of guselkumab both in the proportion of patients who achieved remission by week 24 and in the analysis of the time to remission.

In view of the reduced certainty of conclusions of the results (see Section 2.4.2.2), there was an indication of an added benefit of guselkumab compared with adalimumab for remission (PASI 100) for each of both analyses.

This deviates from the assessment of the company, which derived proof of an added benefit for the outcome "remission" (PASI 100) for the meta-analysis of the studies VOYAGE 1 and VOYAGE 2.

Patient-reported symptoms (PSSD)

The Symptom score 0 and the Sign score 0 were considered individually for the outcome "PSSD". Both the proportions of patients with a Symptom or Sign score of 0 at week 24 and the time to achieving a Symptom or Sign score of 0 were considered. Regarding the Symptom score 0 and the Sign score 0, both analyses showed statistically significant differences in favour of guselkumab in the meta-analysis.

However, the results from the analyses using the proportions of the patients with Symptom score 0 or Sign score 0 were highly biased due to the large proportion of imputed values. For this reason, results of sensitivity analyses conducted by the Institute were additionally considered for the responder analyses at week 24 (see Section 2.6.2.2 of the full dossier assessment). The result of these analyses continued to show a statistically significant difference in favour of guselkumab both for the Symptom and the Sign score 0, despite reduced effect size. Hence the result was robust.

In view of the reduced certainty of conclusions of the results (see Section 2.4.2.2), there was an indication of an added benefit of guselkumab versus adalimumab for the proportion of patients with PSSD Symptom score 0 and PSSD Sign score 0.

There was a hint of an added benefit of guselkumab versus adalimumab for results from the analysis using the time to achieving a PSSD Symptom score 0 and a PSSD Sign score 0.

This deviates from the assessment of the company, which derived proof of an added benefit for the PSSD (analysed as proportion of the patients with Symptom score 0 or Sign score 0) from the meta-analysis of the studies VOYAGE 1 and VOYAGE 2.

No psoriasis symptoms on the scalp (ss-IGA 0)

The company presented no data for the outcome "no psoriasis symptoms on the scalp" (ss-IGA 0) for the relevant subpopulation. There was no hint of an added benefit of guselkumab in comparison with adalimumab for no psoriasis symptoms on the scalp (ss-IGA 0); an added benefit is therefore not proven.

The company did not include this outcome in its assessment and presented no analyses for the relevant subpopulation.

No psoriasis symptoms on hands and feet (hf-PGA 0)

The company presented no analyses for the outcome "no psoriasis symptoms on the hands and feet" (hf-PGA 0) for the relevant subpopulation. There was no hint of an added benefit of guselkumab in comparison with adalimumab for the outcome "no psoriasis symptoms on the hands and feet" (hf-PGA 0); an added benefit is therefore not proven.

The company did not include this outcome in its assessment and presented no analyses for the relevant subpopulation.

No psoriasis symptoms on the nails (NAPSI 0)

In the course of the study, the outcome "no psoriasis symptoms on the nails" was only recorded in patients who had nail psoriasis at the start of the study. For the outcome "no psoriasis symptoms on the nails" (NAPSI 0), the meta-analysis of the studies showed no statistically significant difference between the treatment arms for this patient group regarding both the analysis of the proportion of patients with NAPSI 0 and for the time to achieving NAPSI 0. Consequently, there was no hint of an added benefit of guselkumab in comparison with adalimumab for NAPSI 0; an added benefit is therefore not proven.

This deviates from the assessment of the company, which presented the results for the outcome "NAPSI 0" in the dossier, but did not consider them in the derivation of the added benefit of guselkumab versus adalimumab.

Health-related quality of life

DLQI (0 or 1)

For health-related quality of life, measured with the DLQI, the meta-analysis of the studies produced a statistically significant difference in favour of guselkumab both for the proportion of patients who achieved a DLQI of 0 or 1 at week 24 and for the time to achieving a DLQI of 0 or 1.

In view of the reduced certainty of conclusions of the results (see Section 2.4.2.2), there was an indication of an added benefit of guselkumab compared with adalimumab for health-related quality of life, measured with the DLQI (0 or 1) for each of both analyses.

This deviates from the assessment of the company, which derived proof of an added benefit for the outcome "DLQI (0 or 1)" for the meta-analysis of the studies VOYAGE 1 and VOYAGE 2.

SF-36

The PCS and the MCS of the SF-36 were considered individually. The mean difference of the change from the start of the study until week 24 of the VOYAGE 2 study was considered for each summary score. A statistically significant difference was shown for the mean difference both of the PCS and of the MCS. The CI for the SMD was not fully outside the irrelevance range [−0.2; 0.2], however. It could therefore not be inferred that the effect was relevant. This resulted in no hint of an added benefit of guselkumab in comparison with adalimumab for the SF-36; an added benefit is therefore not proven.

This deviates from the assessment of the company, which presented the results for the SF-36 in the dossier, but did not consider them in the derivation of the added benefit of guselkumab versus adalimumab.

Side effects

Serious adverse events and discontinuation due to adverse events

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

This concurs with the assessment of the company, which also derived no proof of added benefit for the outcomes "SAEs" and "discontinuation due to AEs".

Specific adverse events

Infections and infestations

The meta-analysis of the studies showed no statistically significant difference between the treatment groups for the outcome "infections and infestations". Hence for the outcome "infections and infestations", there was no hint of greater or lesser harm from guselkumab in comparison with adalimumab; greater or lesser harm is therefore not proven.

This concurs with the assessment of the company, which derived no proof of an added benefit for this outcome.

If applicable, further specific adverse events

A selection of further specific AEs based on the documents provided by the company in the dossier was not possible. It can only be excluded that potential specific AEs were serious or resulted in discontinuation of treatment (see Section 2.6.2.4.3 of the full dossier assessment). Hence there was no hint of greater or lesser harm from guselkumab in comparison with adalimumab; greater or lesser harm is therefore not proven.

2.4.2.4 Subgroups and other effect modifiers

The company investigated a number of subgroup characteristics in its assessment. The following subgroup characteristics investigated by the company were considered relevant in the present benefit assessment:

- age (< 45 years/≥ 45 years to < 65 years/≥ 65 years)
- sex (female/male)
- disease severity (PASI < 20/PASI ≥ 20)
- ethnicity (white, black or African American, Asian, American Indian or Native Alaskan, Native Hawaiian or Pacific islander, other ethnicities, several ethnicities, unknown, not reported)
- country (Canada, USA; Hungary, Poland, Russia, Germany, Spain, Australia)
- prior biological treatment (yes/no)

All subgroup characteristics and cut-off values mentioned were prespecified.

The company presented subgroup analyses for the following relevant outcomes: PASI 100, PSSD; NAPSI 0, DLQI (0 or 1), SF-36, SAEs, discontinuation due to AEs, and infections and infestations. The company presented no data for the relevant subpopulation for the outcomes "hf-PGA 0" and "ss-IGA 0" and did not use these outcomes for the benefit assessment. Hence no results on subgroup analyses were available for these outcomes.

The company conducted separate interaction tests for each study in analyses on binary outcomes (proportion of patients with event) and continuous outcomes (mean change from the start of the study to week 24). It only assumed an effect modification if there was an effect modification both within the VOYAGE 1 study and within the VOYAGE 2 study (p-value of the interaction test < 0.05 in each case). Due to the approach of a replicated significant result, the significance level was not exhausted and the power was smaller than it could have been (see Section 2.6.2.2 of the full dossier assessment).

Hence the present benefit assessment checked whether a significant effect modification at the level of 0.2 was present in both studies. If this was the case, an interaction test was conducted at the meta-level of both studies using Q test. Hereinafter, the results are only presented for subgroup analyses with an effect modification with a statistically significant interaction between treatment and subgroup characteristic in the studies included (p-value < 0.05). In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

In accordance with the methods described above, no relevant effect modification was identified for the present research question. This concurs with the company's assessment.

2.4.3 Probability and extent of added benefit

The derivation of probability and extent of the added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

2.4.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4.2 (see Table 30). The conclusions on the extent for outcomes for which both the analyses using the proportion of patients with event and the analyses using time to event were used, were aggregated to one conclusion for each outcome.

Determination of the outcome category for the outcomes "remission" (PASI 100) and "patient-reported symptoms" (PSSD)

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

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

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

The data recorded in the beginning of the study were used for assessing the severity of the symptoms. In the relevant subpopulation, just over half of the patients had a PASI of ≥ 20 (VOYAGE 1: 51% versus 53%; VOYAGE 2: 56% versus 52% [in each case guselkumab versus adalimumab]). Hence the PASI scores for the majority of the participants tended to be in a serious range [6,7]. The outcome "remission" (PASI 100) for these patients was therefore allocated to the category of serious/severe symptoms/late complications.

This allocation concurs with the assessment of the company, which allocated the outcome "remission" (PASI 100) also to the category "serious/severe symptoms/late complications".

Determination of the outcome category for the outcome "patient-reported symptoms" (PSSD)

As with the outcome "remission" (PASI 100) described above, the allocation of patient-reported symptoms (PSSD) to the outcome category (serious or non-serious) depends on the patients' initial situation. The PSSD Symptom score measures the symptoms of itch, pain, stinging, burning and skin tightness, and the PSSD Sign score measures the symptoms of skin dryness, cracking, scaling, shedding or flaking, redness and bleeding.

Regarding the severity of the symptoms, however, there is no information for the PSSD as to when these are rated as severe. Since the company also provided no information on the allocation of the severity grade based on the PSSD instrument, patient-reported symptoms (PSSD) were allocated to the category of non-serious/non-severe symptoms/late complications.

This allocation deviates from the assessment of the company, which allocated the outcome "PSSD" to the category "serious/severe symptoms/late complications".

Table 30: Extent of added benefit at outcome level: guselkumab vs. adalimumab (research question B)

Outcome category **Outcome**	**Guselkumab vs. adalimumab** **Proportion of events or median time to event or mean value at week 24** **Effect [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser benefit/added benefit not proven
Morbidity		
Remission (PASI 100)		
Proportion of patients with remission	40.0–43.9% vs. 24.2–26.9%[c] RR: 1.60 [1.27; 2.02]; p < 0.01 RR: 0.63 [0.50; 0.79][d] probability: "indication"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "non-quantifiable", at least "considerable"
Time to remission	Median: NA vs. NA HR: 1.75 [1.35; 2.27]; p < 0.01 HR: 0.57 [0.44; 0.74][d] probability: "indication"	
Patient-reported symptoms (PSSD)		
Proportion of patients with Symptom score 0	27.5 – 29.3% vs. 12.9 – 15.6%[c]	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"[f]
NRI analysis	RR: 1.92 [1.40; 2.64]; p < 0.01 RR: 0.52 [0.38; 0.71][d]	
Sensitivity analysis[e]	RR: 1.62 [1.18; 2.22]; p = 0.003 RR: 0.62 [0.45; 0.85][d] probability: "indication"	
Time to achievement of Symptom score 0	Median: NA vs. NA HR: 1.87 [1.38; 2.54]; p < 0.01 HR: 0.53 [0.39; 0.72][d] probability: "hint"	
Proportion of patients with Sign score 0	23.3–23.4% vs. 9.6–9.8%[c]	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Added benefit, extent: "considerable"[g]
NRI analysis	RR: 2.23 [1.53; 3.25]; p < 0.01 RR: 0.45 [0.31; 0.65][d]	
Sensitivity analysis[e]	RR: 1.92 [1.30; 2.84]; p < 0.001 RR: 0.52 [0.35; 0.77][d] probability: "indication"	
Time to achievement of Sign score 0	Median: NA vs. NA HR: 1.86 [1.32; 2.61]; p < 0.01 HR: 0.54 [0.38; 0.76][d] probability: "hint"	

(continued)

Table 30: Extent of added benefit at outcome level: guselkumab vs. adalimumab (research question B) (continued)

Outcome category **Outcome**	**Guselkumab vs. adalimumab** **Proportion of events or median time to event or mean value at week 24** **Effect [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Morbidity		
No psoriasis symptoms on the scalp (ss-IGA 0)	No analysis available for the relevant subpopulation	Lesser benefit/added benefit not proven
No psoriasis symptoms on hands and feet (hf-PGA 0)	No analysis available for the relevant subpopulation	Lesser benefit/added benefit not proven
No psoriasis symptoms on the nails (NAPSI 0)		
Proportion of patients with NAPSI 0[h]	20.6–36.1% vs. 29.5–29.9%[c] RR: 0.97 [0.71; 1.32]; p = 0.861	*For patients with nail psoriasis:* lesser benefit/added benefit not proven
Time to achievement of NAPSI 0	NA vs. NA HR 0.86 [0.58; 1.27]; p = 0.43	
Health-related quality of life		
DLQI (0 or 1)		
Proportion of patients with DLQI (0 or 1)	51.7–54.7% vs. 32.6–34.7%[c] RR: 1.60 [1.33; 1.92]; p < 0.01 RR: 0.63 [0.52; 0.75][d, i] probability: "indication"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable"
Time to achievement of DLQI (0 or 1)	Median: 5.49–5.52 months vs. NA HR: 1.59 [1.25; 2.04]; p < 0.01 HR: 0.63 [0.49; 0.80][d] probability: "indication"	
SF-36[j]		
PCS	52.81 vs. 51.37 MD: 2.2 [0.8; 3.6]; p = 0.002 SMD: 0.33 [0.1; 0.6][k]	Lesser benefit/added benefit not proven
MCS	49.27 vs. 46.08 MD: 2.6 [0.9; 4.3]; p = 0.003 SMD: 0.31 [0.1; 0.5][k]	Lesser benefit/added benefit not proven
Side effects		
SAEs	2.0–3.3% vs. 4.2–4.5%[c] RR: 0.63 [0.28; 1.40]; p = 0.26	Greater/lesser harm not proven
Discontinuation due to AEs	1.3–1.5% vs. 3.0–3.6%[c] RR: 0.43 [0.15; 1.22]; p = 0.11	Greater/lesser harm not proven
Infections and infestations	33.8–34.0% vs. 31.8–36.7%[c] RR: 0.99 [0.80; 1.23]; p = 0.94	Greater/lesser harm not proven
If applicable, further specific AEs	Comprehensive identification of specific AEs not guaranteed	

(continued)

Table 30: Extent of added benefit at outcome level: guselkumab vs. adalimumab (research question B) (continued)

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Minimum and maximum proportions of events in each treatment arm in the studies included.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: Due to the large proportion of imputed values in the analysis, the robustness of the results was checked in a sensitivity analysis conducted by the Institute (see Section 2.6.2.2 of the full dossier assessment).
f: In the overall consideration, an indication of an added benefit is derived for the PSSD Symptom score 0 due to the consistent results of both operationalizations. Due to the deviations in the results of different analyses using the proportion of patients with event, the extent of the added benefit is non-quantifiable.
g: In the overall consideration, an indication of an added benefit is derived for the PSSD Sign score 0 due to the consistent results of both operationalizations.
h: The analysis includes only patients with nail psoriasis at the start of the study.
i: $CI_u = 0.753$; the company's analysis was replicated to determine the third digital place (meta-analysis with fixed effect; inverse variance method).
j: The SF-36 was not recorded in the VOYAGE 1 study. Analyses are only available for the VOYAGE 2 study.
k: If the CI for the SMD is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, it cannot be derived that a relevant effect is present.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; DLQI: Dermatology Life Quality Index; hf-PGA: Physician Global Assessment of Hands and/or Feet; HR: hazard ratio; MCS: Mental Component Summary; MD: mean difference; NA: not achieved; NAPSI: Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index; PCS: Physical Component Summary; PSSD: Psoriasis Symptoms and Signs Diary; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SMD: standardized mean difference; ss-IGA: Scalp-specific Investigator Global Assessment; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 31 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 31: Positive and negative effects from the assessment of guselkumab in comparison with adalimumab

Positive effects	**Negative effects**
Morbidity ▪ Serious/severe symptoms/late complications ▫ remission (PASI 100): indication of an added benefit – extent "non-quantifiable", at least "considerable" ▪ Non-serious/non-severe symptoms/late complications ▫ patient-reported symptoms (PSSD): - Symptom score 0: indication of an added benefit – extent: "non-quantifiable" - Sign score 0: indication of an added benefit – extent: "considerable"	–
Health-related quality of life ▪ DLQI (0 or 1): indication of an added benefit – extent: "considerable"	
Morbidity: ▪ no psoriasis symptoms on the scalp: no data presented by the company ▪ no psoriasis symptoms on hands and feet: no data presented by the company	
If applicable, further specific AEs: no conclusive assessment possible based on the data presented by the company	
AE: adverse event; DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index; PSSD: Psoriasis Area and Severity Index	

Overall, only positive effects were found for guselkumab in comparison with adalimumab in the outcome categories of morbidity and health-related quality of life, each with the probability "indication". In each case, the extent was considerable or non-quantifiable.

No analyses for the relevant subpopulation were available for the assessment of the morbidity outcomes of no psoriasis symptoms on the scalp and no psoriasis symptoms on the hands and feet. There were also no data for the choice of further specific AEs. However, it can be excluded that potential specific AEs were serious or resulted in discontinuation of treatment. Nevertheless, no conclusive assessment based on available data is possible for further positive and negative effects.

Nonetheless, due to the notable positive effects of guselkumab – particularly the effect size regarding remission (PASI 100) – it is not assumed in the present data situation that the presence of the missing information on the outcomes "no psoriasis symptoms on the scalp" or "no psoriasis symptoms on the hands and feet" and on the further specific AEs would change the overall conclusion on the added benefit.

In summary, there is an indication of a considerable added benefit of guselkumab in comparison with adalimumab for adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or PUVA, or with contraindication or intolerance to such treatments. This deviates from the assessment of the company, which derived proof of major added benefit of guselkumab in comparison with adalimumab.

2.4.4 List of included studies

VOYAGE 1

Blauvelt A, Papp KA, Griffiths CE, Randazzo B, Wasfi Y, Shen YK et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol 2017; 76(3): 405-417.

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Janssen Research & Development. A phase 3, multicenter, randomized, double-blind, placebo and active comparator-controlled study evaluating the efficacy and safety of guselkumab for the treatment of subjects with moderate to severe plaque-type psoriasis (VOYAGE 1): study CNTO1959PSO3001; clinical protocol [unpublished]. 2016.

Janssen Research & Development. A phase 3, multicenter, randomized, double-blind, placebo and active comparator-controlled study evaluating the efficacy and safety of guselkumab for the treatment of subjects with moderate to severe plaque-type psoriasis (VOYAGE 1): study CNTO1959PSO3001; statistical analysis plan [unpublished]. 2016.

Janssen Research & Development. A phase 3, multicenter, randomized, double-blind, placebo and active comparator-controlled study evaluating the efficacy and safety of guselkumab for the treatment of subjects with moderate to severe plaque-type psoriasis (VOYAGE 1): study CNTO1959PSO3001; 48-week clinical study report [unpublished]. 2016.

Janssen Research & Development. A phase 3, multicenter, randomized, double-blind, placebo and active comparator-controlled study evaluating the efficacy and safety of guselkumab for the treatment of subjects with moderate to severe plaque-type psoriasis (VOYAGE 1): study CNTO1959PSO3001; statistical analysis plan for HTA purposes (Germany, France) [unpublished]. 2016.

Janssen Research & Development. A phase 3, multicenter, randomized, double-blind, placebo and active comparator-controlled study evaluating the efficacy and safety of guselkumab for the treatment of subjects with moderate to severe plaque-type psoriasis (VOYAGE 1): study CNTO1959PSO3001; Zusatzanalysen [unpublished]. 2017.

Janssen-Cilag International. A phase 3, multicenter, randomized, double-blind, placebo and active comparator-controlled study evaluating the efficacy and safety of guselkumab for the treatment of subjects with moderate to severe plaque-type psoriasis [online]. In: EU Clinical Trials Register. [Accessed: 18.12.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-000719-15.

VOYAGE 2

Janssen Research & Development. A study of guselkumab in the treatment of participants with moderate to severe plaque-type psoriasis with randomized withdrawal and retreatment (VOYAGE 2): study results [online]. In: ClinicalTrials.gov. 06.11.2017 [Accessed: 18.12.2017]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02207244.

Janssen Research & Development. A study of guselkumab in the treatment of participants with moderate to severe plaque-type psoriasis with randomized withdrawal and retreatment (VOYAGE 2): full text view [online]. In: ClinicalTrials.gov. 06.11.2017 [Accessed: 18.12.2017]. URL: https://ClinicalTrials.gov/show/NCT02207244.

Janssen Research & Development. A phase 3, multicenter, randomized, double-blind, placebo and active comparator-controlled study evaluating the efficacy and safety of guselkumab for the treatment of subjects with moderate to severe plaque-type psoriasis with randomized withdrawal and retreatment (VOYAGE 2): study CNTO1959PSO3002; clinical protocol [unpublished]. 2015.

Janssen Research & Development. A phase 3, multicenter, randomized, double-blind, placebo and active comparator-controlled study evaluating the efficacy and safety of guselkumab for the treatment of subjects with moderate to severe plaque-type psoriasis with randomized withdrawal and retreatment (VOYAGE 2): study CNTO1959PSO3002; statistical analysis plan [unpublished]. 2016.

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Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. J Am Acad Dermatol 2017; 76(3): 418-431.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of guselkumab in comparison with the ACT is summarized in Table 32.

Table 32: Guselkumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
A	Adult patients with moderate to severe plaque psoriasis who are candidates for systemic treatment[b]	**Fumaric acid esters** or ciclosporin or methotrexate or phototherapy (balneo-phototherapy, oral PUVA, NB-UVB) or secukinumab[c]	Indication of considerable added benefit
B	Adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or PUVA, or with contraindication or intolerance to such treatments	**Adalimumab** or infliximab or ustekinumab or secukinumab[c]	Indication of considerable added benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The population includes all patients in the approved therapeutic indication, except for the patients mentioned in research question B.
c: Dosage of the ACT was to concur with the recommendations of the relevant SPC. A dose-fair comparison under exhaustion of the approval-compliant dosage (if tolerated) was to be conducted. It is a precondition that topical treatment alone is inadequate for the patients treated.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); PUVA: psoralen and ultraviolet-A light; SPC: Summary of Product Characteristics

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

References for English extract

Please see full dossier assessment for full reference list.

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

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