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Guselkumab (plaque psoriasis) –

Addendum to Commission A17-60[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CI	confidence interval
DLQI	Dermatology Life Quality Index
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
hf-PGA	Physician Global Assessment of Hands and/or Feet
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
NAPSI	Nail Psoriasis Severity Index
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PSSD	Psoriasis Symptoms and Signs Diary
PT	Preferred Term
PUVA	psoralen and ultraviolet-A light
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
SMD	standardized mean difference
SOC	System Organ Class
ss-IGA	Scalp-specific Investigator Global Assessment

1 Background

On 9 April 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-60 (Guselkumab – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented results of the subpopulations of the randomized controlled trials (RCTs) VOYAGE 1 and VOYAGE 2 for the assessment of research question B of the benefit assessment (adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or oral psoralen and ultraviolet-A light [PUVA], or with contraindication or intolerance to such treatments). Both studies were included in the assessment. It was unclear, however, whether, in compliance with the requirement of the G-BA, the company had only considered patients with inadequate response to prior systemic treatment or with intolerance or contraindication to such treatment when forming its subpopulations. In addition, the company unnecessarily excluded all patients with a Dermatology Life Quality Index (DLQI) ≤ 10 at the start of the study when forming the population. This definition of the study population was used as sufficient approximation to the population relevant for research question B; the overall certainty of conclusions based on this definition was reduced, however. Detailed reasons can be found in dossier assessment A17-60 [1].

Furthermore, the company had presented no results for the following outcomes in its dossier: no psoriasis symptoms on the scalp (scalp-specific Investigator Global Assessment [ss-IGA] 0), no psoriasis symptoms on hands and feet (Physician Global Assessment of Hands and/or Feet [hf-PGA] 0), and common adverse events (AEs) for the choice of specific AEs.

In its comment, the company submitted supplementary information, which went beyond the information provided in the dossier, to prove the added benefit [2-4]. The G-BA commissioned IQWiG to assess the analyses of the studies VOYAGE 1 and VOYAGE 2 presented by the company in the commenting procedure and with the meta-analysis of both studies on the newly created patient population B under consideration of the information provided in the comment, including the data subsequently submitted on the outcomes "ss-IGA" and "hf-PGA" for patient population B.

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

2 Assessment

2.1 Relevant subpopulation of the studies VOYAGE 1 and VOYAGE 2

The studies VOYAGE 1 and VOYAGE 2 were randomized, double-blind studies in 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. The relevant study arms compared guselkumab with adalimumab. The design of these studies and the characteristics of the interventions are presented in dossier assessment A17-60 [1].

Only subpopulations of the studies VOYAGE 1 and VOYAGE 2 are relevant for answering research question B. These subpopulations comprise 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. However, 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. In addition, the company unnecessarily excluded all patients with a DLQI $\leq$ 10 at the start of the study when forming the population.

The company's comment [2] and the discussion in the oral hearing [5] revealed that the subpopulation formed by the company was composed of all pretreated patients who had already received systemic treatment. The company did not consider the reasons for treatment discontinuation in accordance with the G-BA's definition of the subpopulation. With its comment, the company presented results for the newly defined subpopulation of the studies. The newly defined subpopulation is an adequate representation of the patient population for research question B and is assessed below. The new definition of the study population is an adequate response to the uncertainties regarding the formation of the subpopulation addressed in the dossier assessment. Based on the meta-analysis of both studies, at most proof, e.g. of an added benefit, can therefore be derived.

2.2 Patient characteristics and risk of bias across outcomes

Table 1 shows the characteristics of the patients in the relevant subpopulation subsequently submitted by the company in the comment.

Table 1: Characteristics of the study population – RCT, direct comparison: guselkumab vs. adalimumab (research question B)

Study Characteristics Category	**Guselkumab**	**Adalimumab**
VOYAGE 1	N = 170	N = 179
Age [years], mean (SD)	ND[a]	ND[a]
Sex [F/M], %	27.1/72.9	23.5/76.5
Ethnicity, n (%)		
White	137 (80.6)	144 (80.4)
Other[b]	33 (19.4)	35 (19.6)
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 (%)	73 (42.9)	105 (58.7)
DLQI, mean (SD)	ND	ND
DLQI ≥ 10, n (%)	119 (70.0)	137 (76.5)
IGA[d], n (%)		
0 to 3 (none to moderate)	136 (80.0)	122 (68.2)
4 (severe)	34 (20.0)	57 (31.8)
Psoriatic arthritis, n (%)	37 (21.8)	36 (20.1)
Pretreatment with, n (%)		
Phototherapy	122 (71.6)	119 (66.5)
Non-biological systemic treatment	163 (95.9)	173 (96.6)
Biologics	44 (25.9)	45 (25.1)
Treatment discontinuation, n (%)	2 (1.2[e])	5 (2.8[e])
Study discontinuation, n (%)	ND	ND

(continued)

Table 1: Characteristics of the study population – RCT, direct comparison: guselkumab vs. adalimumab (research question B) (continued)

Study Characteristics Category	**Guselkumab**	**Adalimumab**
VOYAGE 2	N = 294	N = 138
Age [years], mean (SD)	ND[f]	ND[f]
Sex [F/M], %	28.6/71.4	29.7/70.3
Ethnicity, n (%)		
White	245 (83.3)	115 (83.3)
Other[b]	49 (16.7)	23 (16.7)
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]
PASI, mean (SD)	ND	ND
PASI ≥ 20, n (%)	149 (50.7)	65 (47.1)
DLQI, mean (SD)	ND	ND
DLQI ≥ 10, n (%)	232 (78.9)	106 (76.8)
IGA[d], n (%)		
0 to 3 (none to moderate)	229 (77.9)	111 (80.4)
4 (severe)	65 (22.1)	27 (19.6)
Psoriatic arthritis, n (%)	62 (21.1)	29 (21.0)
Pretreatment with, n (%)		
Phototherapy	213 (72.4)	96 (69.6)
Non-biological systemic treatment	284 (96.6)	131 (94.9)
Biologics	65 (22.1)	26 (18.8)
Treatment discontinuation, n (%)	3 (1.0[e])	5 (3.6[e])
Study discontinuation, n (%)	ND	ND

(continued)

Table 1: Characteristics of the study population – RCT, direct comparison: guselkumab vs. adalimumab (research question B) (continued)

a: The company only presented categorial information on age [years]. Guselkumab: < 45: 55.3%; ≥ 45 to < 65: 38.2%; ≥ 65: 6.5%. Adalimumab: < 45: 53.1%; ≥ 45 to < 65: 42.5%; ≥ 65: 4.5%. 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: 43.5%; ≥ 15: 56.5%. Adalimumab: < 15: 40.8%; ≥ 15: 59.2%. 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: Institute's calculation.
f: The company only presented categorial information on age [years]. Guselkumab: < 45: 51.4%; ≥ 45 to < 65: 45.2%; ≥ 65: 3.4%. Adalimumab: < 45: 58.0%; ≥ 45 to < 65: 40.6%; ≥ 65: 1.4%. 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: 38.4%; ≥ 15: 61.6%. Adalimumab: < 15: 48.6%; ≥ 15: 51.4%. The mean disease duration in the total population was 17.9 years for guselkumab and 17.6 years for adalimumab.

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

In both study, most participants were younger than 45 years, male and white. The disease characteristics of the patients in the subpopulation differed in individual characteristics (Psoriasis Area and Severity Index [PASI] ≥ 20 or Investigator Global Assessment) between the study arms within the individual studies and between both studies. Despite these individual differences, the studies were considered sufficiently similar for a meta-analysis.

The risk of bias of the results from the studies VOYAGE 1 and VOYAGE 2 across outcomes was rated as low. This is described in detail in the dossier assessment [1].

2.3 Results

2.3.1 Outcomes included

Table 2 shows for which outcomes data were available in the newly defined subpopulation.

Table 2: 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 (SOC)**
VOYAGE 1 (24/28[c] weeks)	Yes	Yes	Yes	Yes	Yes	No[d]	Yes	No[e]	Yes	Yes	Yes
VOYAGE 2 (24/28[c] weeks)	Yes	Yes	Yes	Yes	Yes	No[d]	Yes	Yes	Yes	Yes	Yes

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 outcomes on the category of side effects were observed until week 28.
d: No usable data, see text for details.
e: Outcome not recorded.

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

With its comment, the company presented results on all outcomes relevant for the benefit assessment (see [1] for the choice of operationalizations and analyses).

The results for the outcome “no psoriasis symptoms on hands and feet” (measured with the hf-PGA 0) were not usable due to the large proportion of patients for whom the outcome was not recorded in the course of the study. This is justified as follows:

The outcome “no psoriasis symptoms on hands and feet” (hf-PGA 0) was only recorded in the course of the study in patients with psoriasis on hands and feet at the start of the study. The company provided no information on the proportion of these patients in the subpopulation; it

was about 30% (VOYAGE 1) and 25% (VOYAGE 2) in relation to the total population of the studies. Hence no observation was available for an important proportion of the subpopulation. This type of outcome recording only detects positive or unchanged courses of disease, but does not detect deterioration or new occurrence of skin symptoms on the hands and feet in the course of the study. The analyses presented by the company on the outcome "no psoriasis symptoms on hands and feet" (hf-PGA 0) were therefore not used for the benefit assessment.

The same problem as for the hf-PGA also applies to the outcomes "no psoriasis symptoms on the scalp" (ss-IGA 0) and "no psoriasis symptoms on the nails" (Nail Psoriasis Severity Index [NAPSI] 0). These outcomes also were recorded in the course of the study in patients with psoriasis on the scalp or nails. In contrast to the outcome "no psoriasis symptoms on hands and feet" (hf-PGA 0), the results for these 2 outcomes were usable, however.

The company provided no information on the proportion of patients with psoriasis on the scalp for the relevant subpopulation. The proportion in relation to the total population of the studies was about 88% (VOYAGE 1) and 84% (VOYAGE 2), however. Hence the outcome "no psoriasis symptoms on the scalp" was recorded in a majority of the randomized patients. The risk of bias of the results for this outcome was high, however (see Section 2.3.2).

With 63% in each case, the proportion of patients with nail psoriasis at the start of the study was lower than the proportion of patients with psoriasis on the scalp. It was mentioned in the discussion of the oral hearing on the drug ixekizumab [6] that new occurrence of nail involvement tends to be rare in patients with plaque psoriasis. Literature to support this claim was not mentioned, however. The outcome "no psoriasis symptoms on the nails" (NAPSI 0) is therefore presented under the assumption that there is no deterioration of nail psoriasis in the course of the study.

The company also presented results for a comprehensive choice of specific AEs. The company's data contain common AEs and common serious AEs (SAEs) (see Appendix A.4). The common discontinuations due to AEs separated by System Organ Class (SOC) and Preferred Term (PT) were provided by the company only for the VOYAGE 1 study; this did not raise doubts about the comprehensive identification of specific AEs due to the overall low rate of discontinuations due to AEs, however. Based on the methods described in the dossier assessment [1], no further specific AEs were identified.

Comment on the date of analysis

With its comment, the company presented results at week 24 and week 48 for the VOYAGE 1 study, and results at week 24 for the VOYAGE 2 study. As in the dossier assessment [1], results for week 24 were used for the assessment of the newly defined subpopulation. The comparison of the results of the VOYAGE 1 study for week 24 and week 48 for the new definition shows that there were no important deviations between the analyses for the outcomes investigated. Correspondingly, a meta-analysis of the results at week 24 (for side effects at week 28) is possible in the present situation also for the newly defined subpopulation without relevant loss

of information. The results of the VOYAGE 1 study at week 48 are presented in Appendix B as supplementary information.

2.3.2 Risk of bias

Table 3 describes the risk of bias of the results for the relevant outcomes.

Table 3: 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)[b, 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 (SOC)**
VOYAGE 1 24/28[e] weeks	L	L	L	H[f]	H[g]	L	–[h]	L	–[i]	L	L	L
VOYAGE 2 24/28[e] weeks	L	L	L	H[f]	H[g]	L	–[h]	L	L	L	L	L

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.
e: The outcomes on the category of side effects were observed until week 28.
f: Proportion of patients with event: large proportion (> 15%) of imputed values; time to first event: possibly large proportion of potentially informative censorings.
g: Proportion of patients with event: possibly large proportion (> 15%) of imputed values; time to first event: possibly large proportion of patients not actually included (censored at the start of the study).
h: No usable data.
i: Outcome not recorded.

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; SOC: System Organ Class; ss-IGA: Scalp-specific Investigator Global Assessment; vs.: versus

The risk of bias of the results of all outcomes was rated as low in each case, except for patient-reported symptoms (Psoriasis Symptoms and Signs Diary [PSSD]) and no psoriasis symptoms on the scalp (ss-IGA 0).

For the analyses of the PSSD 0 using the proportion of patients with event, the high risk of bias resulted from the large proportion of imputed values (> 15%). There was a high risk of bias, which was caused by the possible large proportion of potentially informative censorings, also for the analyses of the PSSD using the time to event.

There was a high risk also for the outcome "no psoriasis symptoms on the scalp" (ss-IGA 0). As described in Section 2.3.1, the outcome was only recorded during the study in patients with psoriasis on the scalp at the start of the study. This type of outcome recording only detects positive or unchanged courses of disease, but does not detect new occurrence or deterioration in the course of the study. In the comment, the company provided no information on the proportion of these patients in the subpopulation; it was about 88% (VOYAGE 1) and 84% (VOYAGE 2) in relation to the total population of the studies. Hence the outcome was recorded in a majority of the patients. The results for the outcome "no psoriasis symptoms on the scalp" (ss-IGA) were therefore overall usable. The company imputed patients without psoriasis on the scalp in the analysis on the proportion of patients with event as non-responders. In the analysis on the time to event, these patients were censored at the start of the study, according to the company [5]. Furthermore, the company's analyses lacked values for 1.2% of the patients in the guselkumab arm and for 4.5% in the adalimumab arm (see Appendix A.3) so that these values were also imputed or censored. In the analysis on the proportion of patients with event, the overall proportion of imputed values was > 15%, resulting in a high risk of bias. The proportion of patients not actually included in the analysis on the time to event was large, also resulting in a high risk of bias.

No usable data were available for the outcome "no psoriasis symptoms on the scalp" (hf-PGA 0) (see Section 2.3.1); the risk of bias of the results was therefore not assessed.

Overall assessment of the certainty of conclusions

Due to the large proportion of imputed values, there was a high risk of bias for the results from the analyses on the proportion of patients with event at week 24 for patient-reported symptoms (PSSD) and no psoriasis symptoms on the scalp (ss-IGA 0). In the presence of a statistically significant effect, this problem is addressed by sensitivity analyses conducted by the Institute (see also [1]). This analysis can be conducted only for patient-reported symptoms (PSSD). For the ss-IGA, there is no information on the number of patients with psoriasis on the scalp at the start of the study, which would have been necessary for the analysis.

If the result is robust after the check by sensitivity analyses conducted by the Institute, this does not lead to a downgrading of the certainty of conclusions. In case of a result that is not robust, at most an indication, e.g. of an added benefit, can be derived for patient-reported symptoms (PSSD).

2.3.3 Results

Table 4 to Table 9 summarize the results at treatment week 24 or 28 for harm 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.

The company presented Kaplan-Meier curves only for the outcome “remission” (PASI 100); these are presented in Appendix A.1. The forest plots on the sensitivity analyses conducted by the Institute can be found in Appendix A.2.

Table 4: Results (mortality, morbidity, health-related quality of life, dichotomous) – RCT, direct comparison: guselkumab vs. adalimumab, week 24 (research question B)

Outcome category Outcome Study	Guselkumab		Adalimumab		Guselkumab vs. adalimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Mortality					
All-cause mortality					
VOYAGE 1	170	0 (0)	179	0 (0)	-
VOYAGE 2	294	0 (0)	138	0 (0)	-
Morbidity					
PASI[b]					
Remission (PASI 100)					
VOYAGE 1	170	77 (45.3)	179	50 (27.9)	1.61 [1.21; 2.15]; < 0.001
VOYAGE 2	294	131 (44.6)	138	33 (23.9)	1.83 [1.33; 2.54]; < 0.001
Total					1.70 [1.37; 2.11]; < 0.01[c]
PASI 90[b]					
VOYAGE 1	*170*	*139 (81.8)*	*179*	*104 (58.1)*	*1.38 [1.20; 1.59]; < 0.001*
VOYAGE 2	*294*	*228 (77.6)*	*138*	*81 (58.7)*	*1.31 [1.13; 1.52]; < 0.001*
Total					*1.35 [1.22; 1.49]; < 0.01[c]*
PASI 75[b]					
VOYAGE 1	*170*	*158 (92.9)*	*179*	*133 (74.3)*	*1.23 [1.12; 1.35]; < 0.001*
VOYAGE 2	*294*	*273 (92.9)*	*138*	*103 (74.6)*	*1.23 [1.11; 1.37]; < 0.001*
Total					*1.23 [1.15; 1.32]; < 0.01[c]*
Patient-reported symptoms (PSSD)					
Symptom score 0[b]					
VOYAGE 1	170	53 (31.2)	179	32 (17.9)	1.73 [1.17; 2.56]; 0.005
VOYAGE 2	294	79 (26.9)	138	22 (15.9)	1.74 [1.15; 2.63]; 0.007
Total					1.73 [1.31; 2.31]; < 0.01[c]
Sensitivity analysis[d]					
VOYAGE 1					1.32 [0.93; 1.88]; NC
VOYAGE 2					1.28 [0.86; 1.91]; NC
Total					1.30 [1.00; 1.70]; 0.049[e]

(continued)

Table 4: 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		Adalimumab		Guselkumab vs. adalimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Sign score 0[b]					
VOYAGE 1	170	46 (27.1)	179	19 (10.6)	2.47 [1.50; 4.08]; < 0.001
VOYAGE 2	294	64 (21.8)	138	14 (10.1)	2.14 [1.27; 3.59]; 0.003
Total					2.31 [1.61; 3.31]; < 0.01[c]
Sensitivity analysis[d]					
VOYAGE 1					1.73 [1.07; 2.80]; NC
VOYAGE 2					1.54 [0.91; 2.61]; NC
Total					1.64 [1.15; 2.34]; 0.006[e]
No psoriasis symptoms on the scalp (ss-IGA 0)[b, f]					
VOYAGE 1	170	104 (61.2)	179	91 (50.8)	1.24 [1.07; 1.44]; 0.003
VOYAGE 2	294	167 (56.8)	138	61 (44.2)	1.10 [0.97; 1.25]; 0.145
Total					1.16 [1.05; 1.27]; < 0.01[c]
No psoriasis symptoms on hands and feet (hf-PGA 0)[g]					
				No usable data[h]	
Health-related quality of life					
DLQI (0 or 1)[b]					
VOYAGE 1	170	100 (58.8)	179	76 (42.5)	1.39 [1.13; 1.71]; 0.002
VOYAGE 2	294	166 (56.5)	138	49 (35.5)	1.58 [1.24; 2.02]; < 0.001
Total					1.47 [1.25; 1.72]; < 0.01[c]

(continued)

Table 4: 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: Meta-analysis with fixed effect (inverse variance method).
d: 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 [7]).
e: Institute's calculation; meta-analysis with fixed effect (inverse variance method).
f: According to the CSR, the outcome was only recorded during the study in patients with psoriasis on the scalp at the start of the study. The proportion of these patients in the subpopulation is unclear; it is about 88% (VOYAGE 1) and 84% (VOYAGE 2) in relation to the total population of the studies.
g: According to the CSR, the outcome was only recorded during the study in patients with psoriasis on the hands and feet at the start of the study. The proportion of these patients in the subpopulation is unclear; it is about 30% (VOYAGE 1) and 25% (VOYAGE 2) in relation to the total population of the studies.
h: Proportion of the patients for whom the outcome was not recorded is too high.

CI: confidence interval; CSR: clinical study report; DLQI: Dermatology Life Quality Index; hf-PGA: Physician Global Assessment of Hands and/or Feet; n: number of patients with 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 5: 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	170	4.67 [3.94; NC] ND	179	NA ND	1.76 [1.26; 2.45]; < 0.001
VOYAGE 2	294	NA [4.67; NC] ND	138	NA ND	2.06 [1.44; 2.95]; < 0.001
Total					1.89 [1.48; 2.42]; < 0.01[b]
PASI 90					
VOYAGE 1	*170*	*2.79 [2.79; 2.89]* *ND*	*179*	*3.02 [2.79; 3.71]* *ND*	*1.43 [1.11; 1.85]; 0.006*
VOYAGE 2	*294*	*2.79 [2.79; 2.86]* *ND*	*138*	*3.71 [2.89; 4.63]* *ND*	*1.85 [1.42; 2.40]; < 0.001*
Total					*1.62 [1.35; 1.95]; < 0.01[b]*
PASI 75					
VOYAGE 1	*170*	*1.87 [1.87; 1.91]* *ND*	*179*	*1.87 [1.87; 2.00]* *ND*	*1.24 [0.98; 1.58]; 0.075*
VOYAGE 2	*294*	*1.87 [1.87; 1.91]* *ND*	*138*	*1.97 [1.87; 2.76]* *ND*	*1.28 [1.01; 1.62]; 0.040*
Total					*1.26 [1.07; 1.49]; < 0.01[b]*
Patient-reported symptoms (PSSD)					
Symptom score 0					
VOYAGE 1	170	NA ND	179	NA ND	1.82 [1.16; 2.86]; 0.009
VOYAGE 2	294	NA ND	138	NA ND	2.10 [1.30; 3.40]; 0.003
Total					1.95 [1.40; 2.70]; < 0.01[b]
Sign score 0					
VOYAGE 1	170	NA ND	179	NA ND	2.57 [1.49; 4.44]; < 0.001
VOYAGE 2	294	NA ND	138	NA ND	2.48 [1.38; 4.45]; 0.002
Total					2.53 [1.70; 3.77]; < 0.01[b]

(continued)

Table 5: 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]
No psoriasis symptoms on the scalp (ss-IGA 0)[c]					
VOYAGE 1	170	3.84 [NC; NC] ND	179	3.75 [NC; NC] ND	1.23 [0.92; 1.66]; 0.167
VOYAGE 2	294	3.94 [NC; NC] ND	138	3.78 [NC; NC] ND	1.37 [1.01; 1.87]; 0.044
Total					1.30 [1.05; 1.60]; 0.02[b]
No psoriasis symptoms on hands and feet (hf-PGA 0)[d]				No usable data[e]	
Health-related quality of life					
DLQI (0 or 1)					
VOYAGE 1	170	3.78 [3.71; 5.52] ND	179	NA [3.94; NC]	1.48 [1.08; 2.02]; 0.014
VOYAGE 2	294	3.78 [3.71; 5.49] ND	138	NA [3.91; NC]	1.40 [1.04; 1.89]; 0.143
Total					1.44 [1.16; 1.78]; < 0.01[b]

a: It is assumed that the calculation of HR, CI and p-value was conducted as follows: Cox proportional hazards model stratified by study centres.
b: Meta-analysis with fixed effect (inverse variance method).
c: According to the CSR, the outcome was only recorded during the study in patients with psoriasis on the scalp at the start of the study. The proportion of these patients in the subpopulation is unclear; it is about 88% (VOYAGE 1) and 84% (VOYAGE 2) in relation to the total population of the studies. According to statements by the company in the oral hearing, the remaining patients were censored at the start of the study [5].
d: According to the CSR, the outcome was only recorded during the study in patients with psoriasis on the hands and feet at the start of the study. The proportion of these patients in the subpopulation is unclear; it is about 30% (VOYAGE 1) and 25% (VOYAGE 2) in relation to the total population of the studies.
e: Proportion of the patients for whom the outcome was not recorded is too high.

CI: confidence interval; CSR: clinical study report; 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; 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 6: 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		Adalimumab		Guselkumab vs. adalimumab
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value
Morbidity					
No psoriasis symptoms on the nails					
NAPSI 0[b]					
VOYAGE 1	108	27 (25.0[c])	112	32 (28.6[c])	0.88 [0.56; 1.36]; NC[d]
VOYAGE 2	182	64 (35.2[c])	88	30 (34.1[c])	1.03 [0.73; 1.47]; NC[d]
Total					0.97 [0.74; 1.27]; 0.812[e]

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 information on how many patients in the relevant subpopulation were affected at the start of the study was explained by the company during the oral hearing [5].
b: NRI analysis.
c: Institute's calculation.
d: Institute's calculation of RR and CI (asymptotic).
e: Institute's calculation; meta-analysis with fixed effect (inverse variance method).

CI: confidence interval; CSR: clinical study report; n: number of patients with (at least one) event; 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 7: 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 score 0					
VOYAGE 1	170	NA ND	179	NA ND	0.69 [0.40; 1.20]; 0.192
VOYAGE 2	294	NA ND	138	NA ND	0.99 [0.63; 1.55]; 0.950
Total					0.86 [0.60; 1.21]; 0.38[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 (in each case about 63% of the patients). According to statements by the company in the oral hearing, the remaining 37% of the patients were censored at the start of the study [5].
b: It is assumed that the calculation of HR, 95% CI and p-value was conducted as follows: 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; RR: relative risk; vs.: versus

Table 8: Results (health-related quality of life, continuous) – RCT, direct comparison: guselkumab vs. adalimumab, week 24 (research question B)

Study Outcome category Outcome Scale	Guselkumab			Adalimumab			Guselkumab vs. adalimumab
	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]
VOYAGE 2							
Health-related quality of life							
SF-36							
PCS[c]	285	46.59 (9.08)	53.20 (7.23)	129	47.94 (8.57)	52.30 (7.84)	1.8 [0.5; 3.1]; 0.006 SMD: 0.27 [0.1; 0.5]
Physical functioning	285	48.12 (9.40)	53.12 (6.84)	129	49.66 (8.79)	52.49 (7.62)	1.6 [0.4; 2.8]
Physical role functioning	285	45.35 (9.97)	51.68 (6.95)	129	45.23 (9.56)	50.44 (7.58)	1.3 [0.0; 2.7]
Bodily pain	285	43.39 (10.74)	53.61 (8.91)	129	45.11 (11.13)	52.00 (10.46)	2.2 [0.4; 4.0]
General health perception	285	44.37 (9.85)	49.97 (9.28)	129	44.64 (9.35)	47.80 (9.70)	2.4 [0.9; 3.9]
MCS[c]	285	43.41 (11.53)	49.74 (8.50)	129	42.54 (11.31)	47.21 (10.47)	2.1 [0.5; 3.7]; 0.010 SMD: 0.25 [0.0; 0.5]
Vitality	285	47.13 (9.53)	53.38 (8.70)	129	46.89 (10.34)	52.10 (10.15)	1.2 [−0.4; 2.8]
Social functioning	285	42.63 (11.47)	51.33 (7.76)	129	42.57 (10.71)	48.35 (9.56)	2.9 [1.3; 4.5]
Emotional role functioning	285	44.62 (11.84)	50.36 (7.90)	129	44.37 (10.86)	48.94 (9.47)	1.5 [−0.0; 3.0]
Mental wellbeing	285	43.13 (10.70)	49.40 (8.46)	129	42.76 (11.16)	46.72 (9.96)	2.4 [0.8; 4.0]

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.
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 9: 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
Side effects					
AEs (supplementary information)					
VOYAGE 1	170	113 (66.5)	178	118 (66.3)	–
VOYAGE 2	294	175 (59.5)	138	84 (60.9)	–
SAEs					
VOYAGE 1	170	5 (2.9)	178	6 (3.4)	0.87 [0.27; 2.81]; > 0.999
VOYAGE 2	294	12 (4.1)	138	6 (4.3)	0.94 [0.36; 2.45]; > 0.999
Total					0.91 [0.43; 1.91]; 0.81[a]
Discontinuation due to AEs					
VOYAGE 1	170	0 (0)	178	5 (2.8)	0.10 [0.01; 1.71][b]; NC
VOYAGE 2	294	4 (1.4)	138	2 (1.4)	0.94 [0.17; 5.06]; > 0.999
Total					0.52 [0.12; 2.25]; 0.385[c]
Infections and infestations					
VOYAGE 1	170	62 (36.5)	178	64 (36.0)	1.01 [0.77; 1.34][b]; NC
VOYAGE 2	294	94 (32.0)	138	48 (34.8)	0.92 [0.69; 1.22][b]; NC
Total					0.97 [0.79; 1.18]; 0.735[c]

a: Meta-analysis with fixed effect (inverse variance method).
b: Institute's calculation of RR and CI (asymptotic); in case of 0 events in one treatment arm, the correction factor of 0.5 was used in the calculation (addition of the value of 0.5 to each cell frequency).
c: Institute's calculation; meta-analysis with fixed effect (inverse variance method).

AE: adverse event; CI: confidence interval; n: number of patients with event; N: number of analysed patients; NC: not calculated; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

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.

This resulted in proof 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 outcome "patient-reported symptoms" (PSSD). The meta-analysis showed statistically significant differences in favour of guselkumab both in the analysis on the proportions of patients with a Symptom or Sign score of 0 at week 24 and in the analysis on the time to achieving a Symptom or Sign score of 0.

The results of both analyses had a high risk of bias due to the large proportion of imputed values or potentially informative censorings, however.

Consequently, 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. Proof of an added benefit of guselkumab versus adalimumab was therefore derived for the analysis on the proportion of patients with event.

An indication of an added benefit of guselkumab versus adalimumab was derived for the analysis on the time to event.

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

For the outcome "no psoriasis symptoms on the scalp" (ss-IGA 0), the meta-analysis showed statistically significant differences in favour of guselkumab both for the analysis on the proportions of patients at week 24 and on the time to achieving ss-IGA 0. The extent of added benefit for each of both operationalizations was no more than marginal, however (see Section 2.3.5.1). Hence overall, there was no hint of an added benefit of guselkumab in comparison with adalimumab for the outcome "no psoriasis symptoms on the scalp" (ss-IGA 0) for both analyses; an added benefit is therefore not proven.

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

The company presented no usable analyses for the outcome "no psoriasis symptoms on the hands and feet" (hf-PGA 0). 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. The outcome was assessed under the assumption that there was no deterioration of nail psoriasis in the course 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 on 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 who achieved a DLQI of 0 or 1 at week 24 and for the time to achieving a DLQI of 0 or 1.

This resulted in proof 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

For the Short Form (36) Health Survey (SF-36), the Physical Component Summary (PCS) and the Mental Component Summary (MCS) were considered individually. A statistically significant difference was shown for the mean difference both of the PCS and of the MCS. The confidence interval (CI) for the standardized mean difference (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, discontinuation due to adverse events, infections and infestations

The meta-analysis of the studies showed no statistically significant differences between the treatment groups for the outcomes "SAEs", "discontinuation due to AEs", and "infections and infestations". Consequently, for the outcomes "SAEs", "discontinuation due to AEs", and "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.

2.3.4 Subgroups and other effect modifiers

With its comment, the company submitted subgroup analyses for the following effect modifiers, which had already been considered relevant in the dossier assessment:

- age (< 45 years/≥ 45 years to < 65 years/≥ 65 years)
- sex (female/male)
- disease severity (PASI < 20/PASI ≥ 20)
- prior biological treatment (yes/no)

The company additionally calculated results of the subgroup analyses for the characteristic "DLQI ≤ 10 versus > 10". This characteristic had been prespecified both for the VOYAGE 1 study and for the VOYAGE 2 study and was also used.

The company still did not present the analyses for the characteristic "ethnicity" with the categories predefined in the study protocols (white, black or African American, Asian, American Indians or Native Alaskans, Native Hawaiians or Pacific Islanders, other ethnicities, several ethnicities, unknown, not reported) and for the characteristic "country" (Canada, USA, Hungary, Poland, Russia, Germany, Spain, Australia).

Hereinafter, the results are only presented for subgroup analyses with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (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. No relevant effect modification was identified for the present research question.

2.3.5 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 [8].

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.

2.3.5.1 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 2.3.3 (see Table 10). 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.

In analogy with dossier assessment A17-60, the data at the start of the study were used for assessing the severity of the symptoms estimated with the PASI. Just over half of all patients (50.2%) in the relevant subpopulation of both studies had a PASI of ≥ 20, corresponding rather to a serious severity grade of this outcome. The outcome "remission" (PASI 100) for these patients was therefore allocated to the category of serious/severe symptoms/late complications.

Regarding the severity of the symptoms, however, the company provided no information for the PSSD and the ss-IGA as to when these are rated as severe. The patient-reported symptoms (PSSD) and the outcome "no psoriasis symptoms on the scalp" (ss-IGA 0) were allocated to the outcome category of non-serious/non-severe symptoms/late complications.

Table 10: 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 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	44.6–45.3% vs. 23.9–27.9%[c] RR: 1.70 [1.37; 2.11]; < 0.01 RR: 0.59 [0.47; 0.73][d] probability: "proof"	Outcome category: serious/severe symptoms/late complications CI_u < 0.75; risk ≥ 5% Added benefit, extent: "major"
Time to remission	Median: 4.67 months vs. NA HR: 1.89 [1.48; 2.42]; < 0.01 HR: 0.53 [0.41; 0.68][d] probability: "proof"	
Patient-reported symptoms (PSSD)		
Proportion of patients with Symptom score 0	26.9–31.2% vs. 15.9–17.9%[c]	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"[f]
NRI analysis	RR: 1.73 [1.31; 2.31]; < 0.01 RR: 0.58 [0.43; 0.76][d]	
Sensitivity analysis[e]	RR: 1.30 [1.00; 1.70]; 0.049 RR: 0.77 [0.59; 1.00][d] probability: "proof"	
Time to achievement of Symptom score 0	Median: NA vs. NA HR: 1.95 [1.40; 2.70]; < 0.01 HR: 0.51 [0.37; 0.71][d] Probability: "indication"	

(continued)

Table 10: 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 at week 24** **Effect [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Patient-reported symptoms (PSSD)		
Proportion of patients with Sign score 0	21.8–27.1% vs. 10.1–10.6%[c]	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"[f]
NRI analysis	RR: 2.31 [1.61; 3.31]; < 0.01 RR: 0.43 [0.30; 0.62][d]	
Sensitivity analysis[e]	RR: 1.64 [1.15; 2.34]; 0.006 RR: 0.61 [0.43; 0.87][d] probability: "proof"	
Time to achievement of Sign score 0	Median: NA vs. NA HR: 2.53 [1.70; 3.77]; < 0.01 HR: 0.40 [0.27; 0.59][d] Probability: "indication"	
No psoriasis symptoms on the scalp (ss-IGA 0)		
Proportion of patients with ss-IGA 0	56.8–61.2% vs. 44.2–50.8% RR: 1.16 [1.05; 1.27]; < 0.01 RR: 0.86 [0.79; 0.95][d]	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[g]
Time to achievement of ss-IGA 0	Median: 3.84–3.94 vs. 3.75–3.78 months HR: 1.30 [1.05; 1.60]; 0.02 HR: 0.77 [0.63; 0.95][d]	
No psoriasis symptoms on hands and feet (hf-PGA 0)	No usable data	lesser benefit/added benefit not proven
No psoriasis symptoms on the nails (NAPSI 0)		
Proportion of patients with NAPSI 0[h]	25.0–35.2% vs. 28.6–34.1%[c] RR: 0.97 [0.74; 1.27]; 0.812	*For patients with nail psoriasis:* lesser benefit/added benefit not proven
Time to achievement of NAPSI 0	NA vs. NA HR: 0.86 [0.60; 1.21]; 0.38	

(continued)

Table 10: 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 at week 24** **Effect [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Health-related quality of life		
DLQI (0 or 1)		
Proportion of patients with DLQI (0 or 1)	56.5–58.8% vs. 35.5–42.5%[c] RR: 1.47 [1.25; 1.72]; < 0.01 RR: 0.68 [0.58; 0.80][d] probability: "proof"	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: 3.78 months vs. NA HR: 1.44 [1.16; 1.78]; < 0.01 HR: 0.69 [0.56; 0.86][d] probability: "proof"	
SF-36[i]		
PCS	53.20 vs. 52.30 MD: 1.8 [0.5; 3.1]; 0.006 SMD: 0.27 [0.1; 0.5][j]	lesser benefit/added benefit not proven
MCS	49.74 vs. 47.21 MD: 2.1 [0.5; 3.7]; 0.010 SMD: 0.25 [0.0; 0.5][j]	lesser benefit/added benefit not proven
Side effects		
SAEs	2.9–4.1% vs. 3.4–4.3%[c] RR: 0.91 [0.43; 1.91]; 0.81	Greater/lesser harm not proven
Discontinuation due to AEs	0–1.4% vs. 1.4–2.8%[c] RR: 0.52 [0.12; 2.25]; 0.385	Greater/lesser harm not proven
Infections and infestations	32.0–36.5% vs. 34.8–36.0%[c] RR: 0.97 [0.79; 1.18]; 0.735	Greater/lesser harm not proven

(continued)

Table 10: 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.
f: Due to the consistent advantage of guselkumab in both operationalizations, proof of an added benefit is derived in the overall consideration. Since there were deviations in the extent of the results of individual analyses, the extent of the added benefit in the overall consideration is non-quantifiable, at most considerable.
g: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
h: The analysis includes only patients with nail psoriasis at the start of the study.
i: The SF-36 was not recorded in the VOYAGE 1 study. Analyses are only available for the VOYAGE 2 study.
j: 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, the presence of a relevant effect cannot be derived.

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

2.3.5.2 Overall conclusion on added benefit

Table 11 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 11: 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): proof of an added benefit – extent: "major" ▪ Non-serious/non-severe symptoms/late complications ▫ patient-reported symptoms (PSSD): - Symptom score 0: proof of an added benefit – extent: "non-quantifiable", at most "considerable" - Sign score 0: proof of an added benefit – extent: "non-quantifiable", at most "considerable"	–
Health-related quality of life ▪ DLQI (0 or 1): proof of an added benefit – extent: "considerable"	
AE: adverse event; DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index; PSSD: Psoriasis Symptom and Sign Diary	

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 "proof". Depending on the outcome, the extent of added benefit is non-quantifiable (at most considerable) to major.

In summary, there is proof of major 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.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure changed the conclusion on the added benefit of guselkumab from dossier assessment A17-60 for research question B: There is proof of major 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. Research question A is not subject of the addendum; the addendum does not change conclusions on the added benefit of guselkumab on research question A.

The following Table 12 shows the result of the benefit assessment of guselkumab under consideration of dossier assessment A17-60 and the present addendum.

Table 12: 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]	**Proof** of **major** 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 G-BA decides on the added benefit.

3 References

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Appendix A – Results, week 24 (research question B)

A.1 – Kaplan-Meier curves

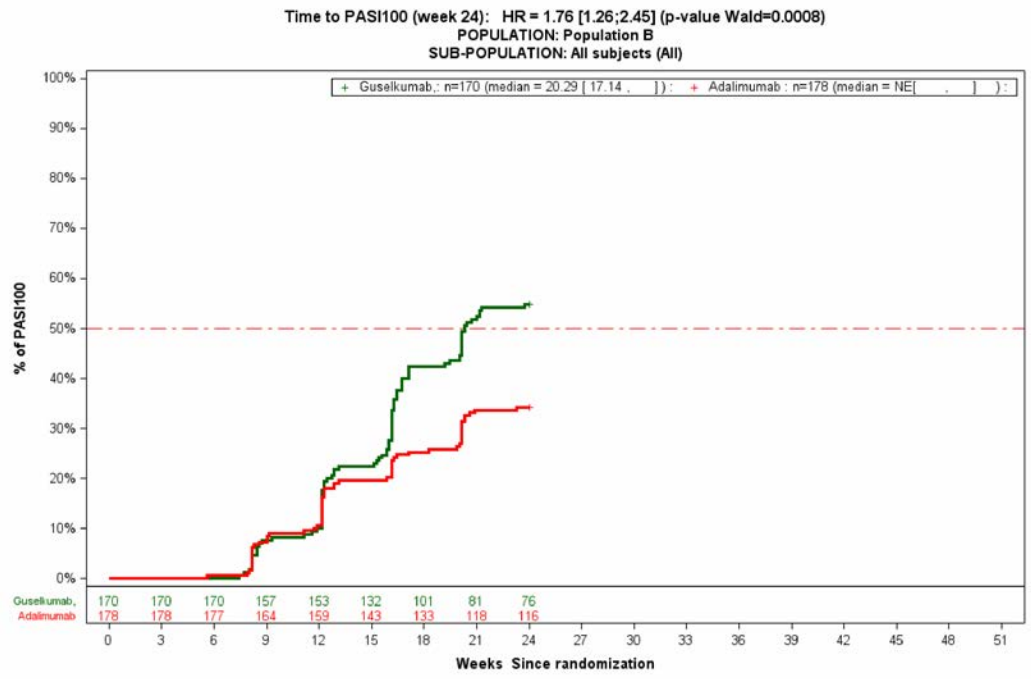

Figure 1: Kaplan-Meier curve for the outcome “remission” (PASI 100) from the VOYAGE 1 study until week 24

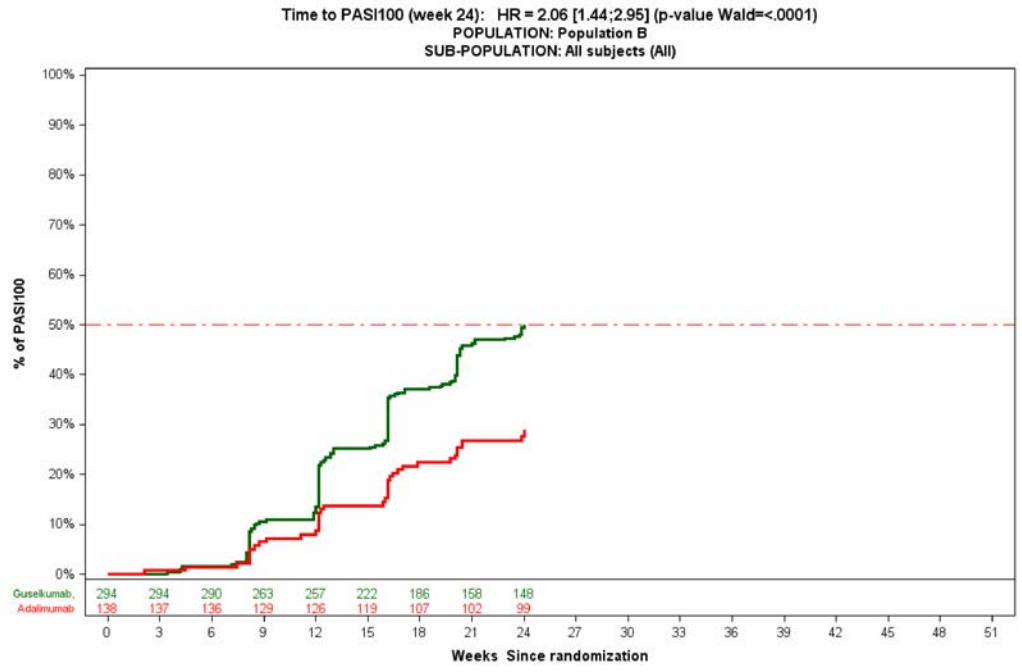

Figure 2: Kaplan-Meier curve for the outcome “remission” (PASI 100) from the VOYAGE 2 study until week 24

A.2 – Sensitivity analyses for the outcome "PSSD"

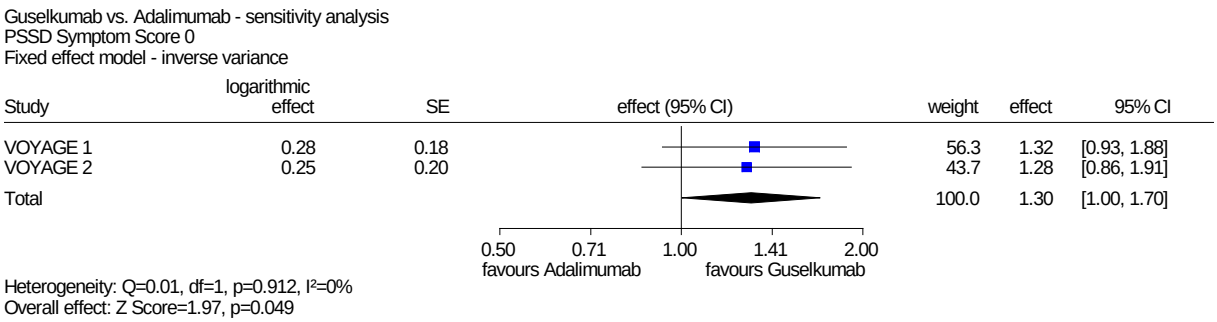

Figure 3: Meta-analysis (fixed-effect model; inverse variance method) for the outcome "patient-based symptoms" (PSSD Symptom score 0), sensitivity analysis

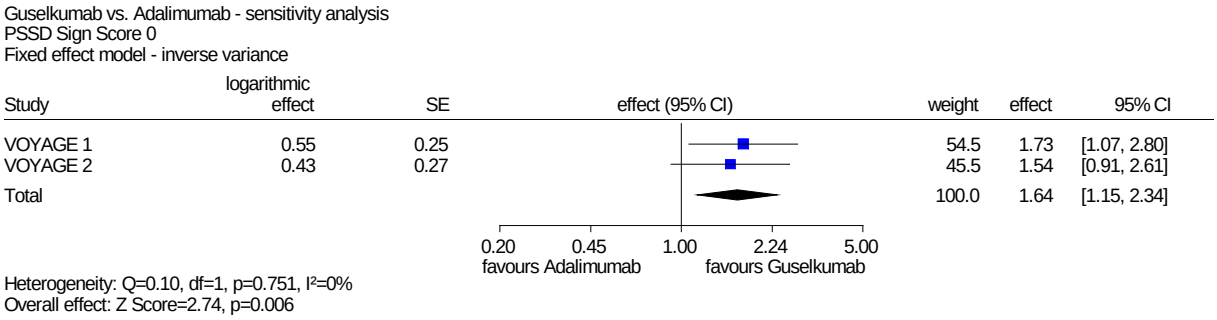

Figure 4: Meta-analysis (fixed-effect model; inverse variance method) for the outcome "patient-based symptoms" (PSSD Sign score 0), sensitivity analysis

A.3 – Missing values

Table 13: Missing values for dichotomous outcomes on morbidity – RCT, direct comparison: guselkumab vs. adalimumab (research question B)

Study Outcome	Missing values, week 24 n (%)		Missing values, week 48 n (%)	
	Guselkumab	**Adalimumab**	**Guselkumab**	**Adalimumab**
VOYAGE 1	N = 170	N = 179	N = 170	N = 179
Remission (PASI 100)	15 (4.6)	17 (5.1)	26 (7.9)	54 (16.2)
Patient-reported symptoms (PSSD)				
Sign score 0	74 (22.5)	88 (26.3)	93 (28.3)	111 (33.2)
Symptom score 0	74 (22.5)	88 (26.3)	93 (28.3)	111 (33.2)
No psoriasis symptoms on the scalp (ss-IGA 0)	14 (4.3)	17 (5.1)	24 (7.3)	54 (16.2)
No psoriasis symptoms on the nails (NAPSI 0)	8 (2.4)	14 (4.2)	16 (4.9)	32 (9.6)
Health-related quality of life (DLQI 0 or 1)	16 (4.9)	17 (5.1)	27 (8.2)	55 (16.5)
VOYAGE 2	N = 294	N = 138	Not applicable	
Remission (PASI 100)	27 (5.4)	14 (5.6)		
Patient-reported symptoms (PSSD)				
Sign score 0	97 (19.6)	60 (24.2)		
Symptom score 0	97 (19.6)	60 (24.2)		
No psoriasis symptoms on the scalp (ss-IGA 0)	25 (5.0)	15 (6.0)		
No psoriasis symptoms on the nails (NAPSI 0)	16 (3.2)	12 (4.8)		
Health-related quality of life (DLQI 0 or 1)	27 (5.4)	18 (7.3)		

DLQI: Dermatology Life Quality Index; n: number of patients in the category; N: number of randomized patients; NAPSI: Nail Psoriasis Severity Index; 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

A.4 – Side effects, week 28

Table 14: Common AEs (in the SOC and in the PT ≥ 3% in at least one study arm) – RCT, direct comparison: guselkumab vs. adalimumab, week 28 (research question B, VOYAGE 1)

Study (time point)	Patients with event n (%)	
SOC[a] **PT[a]**	**Guselkumab** **N = 170**	**Adalimumab** **N = 178**
VOYAGE 1		
Overall rate of AEs	113 (66.5)	118 (66.3)
Infections and infestations	62 (36.5)	64 (36.0)
Nasopharyngitis	33 (19.4)	28 (15.7)
Upper respiratory tract infection	15 (8.8)	16 (9.0)
Bronchitis	2 (1.2)	6 (3.4)
Musculoskeletal and connective tissue disorders	24 (14.1)	20 (11.2)
Arthralgia	13 (7.6)	7 (3.9)
Back pain	6 (3.5)	4 (2.2)
Gastrointestinal disorders	22 (12.9)	14 (7.9)
General disorders and administration site conditions	20 (11.8)	21 (11.8)
Injection site erythema	2 (1.2)	11 (6.2)
Injection site pruritus	1 (0.6)	6 (3.4)
Skin and subcutaneous tissue disorders	20 (11.8)	24 (13.5)
Pruritus	4 (2.4)	8 (4.5)
Nervous system disorders	15 (8.8)	22 (12.4)
Headache	7 (4.1)	10 (5.6)
Investigations	14 (8.2)	13 (7.3)
Injury, poisoning and procedural complications	11 (6.5)	11 (6.2)
Metabolism and nutrition disorders	8 (4.7)	8 (4.5)
Vascular disorders	8 (4.7)	11 (6.2)
Hypertension	6 (3.5)	9 (5.1)
Respiratory, thoracic and mediastinal disorders	6 (3.5)	14 (7.9)
Cough	1 (0.6)	6 (3.4)
Psychiatric disorders	1 (0.6)	6 (3.4)

a: MedDRA version 19.1.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 15: Common AEs (in the SOC and in the PT ≥ 3% in at least one study arm) – RCT, direct comparison: guselkumab vs. adalimumab, week 28 (research question B, VOYAGE 2)

Study (time point)	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Guselkumab** **N = 294**	**Adalimumab** **N = 138**
VOYAGE 2		
Overall rate of AEs	175 (59.5)	84 (60.9)
Infections and infestations	94 (32.0)	48 (34.8)
Nasopharyngitis	31 (10.5)	22 (15.9)
Upper respiratory tract infection	14 (4.8)	5 (3.6)
Pharyngitis	9 (3.1)	2 (1.4)
General disorders and administration site conditions	34 (11.6)	17 (12.3)
Injection site erythema	8 (2.7)	8 (5.8)
Skin and subcutaneous tissue disorders	32 (10.9)	14 (10.1)
Pruritus	12 (4.1)	4 (2.9)
Musculoskeletal and connective tissue disorders	31 (10.5)	8 (5.8)
Arthralgia	11 (3.7)	3 (2.2)
Gastrointestinal disorders	29 (9.9)	11 (8.0)
Diarrhoea	9 (3.1)	3 (2.2)
Nervous system disorders	23 (7.8)	10 (7.2)
Headache	18 (6.1)	4 (2.9)
Investigations	11 (3.7)	5 (3.6)
Injury, poisoning and procedural complications	9 (3.1)	6 (4.3)
Metabolism and nutrition disorders	5 (1.7)	6 (4.3)
Vascular disorders	14 (4.8)	4 (2.9)
Hypertension	10 (3.4)	4 (2.9)
Respiratory, thoracic and mediastinal disorders	15 (5.1)	9 (6.5)

a: MedDRA version 19.1.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 16: All SAEs (SOC/PT) – RCT, direct comparison: guselkumab vs. adalimumab, week 28 (research question B, VOYAGE 1)

Study (time point)	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Guselkumab** **N = 170**	**Adalimumab** **N = 178**
VOYAGE 1		
Overall rate of SAEs	5 (2.9)	6 (3.4)
Cardiac disorders	0 (0)	3 (1.7)
Acute myocardial infarction	0 (0)	1 (0.6)
Cardiac failure	0 (0)	1 (0.6)
Myocardial ischaemia	0 (0)	1 (0.6)
Gastrointestinal disorders	1 (0.6)	0 (0)
Umbilical hernia	1 (0.6)	0 (0)
Hepatobiliary disorders	1 (0.6)	0 (0)
Cholecystitis	1 (0.6)	0 (0)
Musculoskeletal and connective tissue disorders	1 (0.6)	0 (0)
Spondylolisthesis	1 (0.6)	0 (0)
Injury, poisoning and procedural complications	1 (0.6)	1 (0.6)
Clavicle fracture	1 (0.6)	0 (0)
Radius fracture	0 (0)	1 (0.6)
Psychiatric disorders	0 (0)	1 (0.6)
Suicide attempt	0 (0)	1 (0.6)
Renal and urinary disorders	1 (0.6)	0 (0)
Acute kidney injury	1 (0.6)	0 (0)
Skin and subcutaneous tissue disorders	0 (0)	1 (0.6)
Erythrodermic psoriasis	0 (0)	1 (0.6)

a: MedDRA version: unknown.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 17: All SAEs (SOC/PT) – RCT, direct comparison: guselkumab vs. adalimumab, week 28 (research question B, VOYAGE 2)

Study (time point)	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Guselkumab** **N = 294**	**Adalimumab** **N = 138**
VOYAGE 2 (week 28)		
Overall rate of SAEs	12 (4.1)	6 (4.3)
Cardiac disorders	2 (0.7)	1 (0.7)
Angina unstable	1 (0.3)	0 (0)
Myocardial infarction	1 (0.3)	1 (0.7)
Gastrointestinal disorders	0 (0)	1 (0.7)
Inguinal hernia	0 (0)	1 (0.7)
Hepatobiliary disorders	1 (0.3)	0 (0)
Hepatic steatosis	1 (0.3)	0 (0)
Infections and infestations	3 (1.0)	2 (1.4)
Bronchitis	1 (0.3)	0 (0)
Erysipelas	1 (0.3)	0 (0)
Soft tissue infection	1 (0.3)	0 (0)
Disseminated tuberculosis	0 (0)	1 (0.7)
Injection site abscess	0 (0)	1 (0.7)
Investigations	1 (0.3)	0 (0)
Alanine aminotransferase increased	1 (0.3)	0 (0)
Musculoskeletal and connective tissue disorders	1 (0.3)	2 (1.4)
Intervertebral disc protrusion	1 (0.3)	0 (0)
Psoriatic arthropathy	0 (0)	2 (1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	0 (0)
Prostate cancer	1 (0.3)	0 (0)
Nervous system disorders	1 (0.3)	1 (0.7)
Myelitis transverse	1 (0.3)	0 (0)
Epilepsy	0 (0)	1 (0.7)
Renal and urinary disorders	1 (0.3)	0 (0)
Renal colic	1 (0.3)	0 (0)
Reproductive system and breast disorders	1 (0.3)	0 (0)
Ovarian cyst	1 (0.3)	0 (0)

a: MedDRA version: unknown.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

A.5 Supplementary presentation of the results for the outcome "hf-PGA 0"

Table 18: Results for patients with psoriasis on hands and feet at study start (morbidity [hf-PGA 0], dichotomous) – RCT, direct comparison: guselkumab vs. adalimumab, week 24 (research question B)

Outcome category Outcome Study	Guselkumab		Adalimumab		Guselkumab vs. adalimumab
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value[b]
Morbidity					
No psoriasis symptoms on hands and feet (hf-PGA 0)					
VOYAGE 1	170	40 (23.5)	179	29 (16.2)	1.41 [0.95; 2.10]; 0.084
VOYAGE 2	294	59 (20.1)	138	18 (13.0)	1.55 [0.97; 2.47]; 0.060
Total					1.47 [1.08; 1.99]; 0.01[c]

a: According to the CSR, the outcome was only recorded during the study in patients with psoriasis on the hands and feet at the start of the study. The proportion of these patients in the subpopulation is unclear; it is about 30% (VOYAGE 1) and 25% (VOYAGE 2) in relation to the total population of the studies.
b: RR, 95% CI and p-value were determined with the Cochran-Mantel-Haenszel method under consideration of the stratification according to study centres.
c: Meta-analysis with fixed effect (inverse variance method).

CI: confidence interval; CSR: clinical study report; hf-PGA: Physician Global Assessment of Hands and/or Feet; n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 19: Results for patients with psoriasis on hands and feet at study start (morbidity [hf PGA 0], time to event) – RCT, direct comparison: guselkumab vs. adalimumab, week 24 (research question B)

Outcome category **Outcome** **Study**	**Guselkumab**		**Adalimumab**		**Guselkumab vs. adalimumab**
	N[a]	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N[a]**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[b]**
Morbidity					
No psoriasis symptoms on hands and feet (hf-PGA 0)					
VOYAGE 1	170	3.71 [3.71; 3.94] ND	179	NA [3.78; NC] ND	1.60 [0.82; 3.11]; 0.164
VOYAGE 2	294	3.71 [3.71; 3.75] ND	138	3.91 [3.71; NC] ND	2.36 [1.03; 5.41]; 0.042
Total					1.86 [1.11; 3.13]; 0.02[c]

a: According to the CSR, the outcome was only recorded during the study in patients with psoriasis on the hands and feet at the start of the study. The proportion of these patients in the subpopulation is unclear; it is about 30% (VOYAGE 1) and 25% (VOYAGE 2) in relation to the total population of the studies. According to statements by the company in the oral hearing, the remaining patients were censored at the start of the study [5].

b: It is assumed that the calculation of HR, CI and p-value was conducted as follows: Cox proportional hazards model stratified by study centres.

c: Meta-analysis with fixed effect (inverse variance method).

CI: confidence interval; CSR: clinical study report; hf-PGA: Physician Global Assessment of Hands and/or Feet; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; RCT: randomized controlled trial; vs.: versus

Appendix B – Results (supplementary presentation), week 48 (research question B, VOYAGE 1)

B.1 – Results

Table 20: Results (mortality, morbidity, health-related quality of life, dichotomous) – RCT, direct comparison: guselkumab vs. adalimumab, week 48 (research question B, VOYAGE 1)

Study Outcome category	Guselkumab		Adalimumab		Guselkumab vs. adalimumab
Outcome	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
VOYAGE 1					
Mortality					
All-cause mortality	170	0 (0)	179	0 (0)	–
Morbidity					
PASI[b]					
Remission (PASI 100)	170	85 (50.0)	179	48 (26.8)	1.90 [1.45; 2.49]; < 0.001
PASI 90[b]	*170*	*132 (77.6)*	*179*	*104 (58.1)*	*1.31 [1.13; 1.52]; < 0.001*
PASI 75[b]	*170*	*155 (91.2)*	*179*	*128 (71.5)*	*1.25 [1.13; 1.38]; < 0.001*
Patient-reported symptoms (PSSD)					
Symptom score 0[b]	170	56 (32.9)[c]	179	38 (21.2)[c]	1.55 [1.07; 2.24]; 0.016
Sign score 0[b]	170	49 (28.8)[c]	179	30 (16.8)[c]	1.70 [1.12; 2.57]; 0.009
No psoriasis symptoms on the scalp (ss-IGA 0)[b, c]	170	101 (59.4)	179	84 (46.9)	1.30 [1.11; 1.51]; < 0.001
No psoriasis symptoms on hands and feet (hf-PGA 0)[d]	No usable data[e]				
Health-related quality of life					
DLQI (0 or 1)[b]	170	104 (61.2)	179	81 (45.3)	1.36 [1.11; 1.66]; 0.002

(continued)

Table 20: Results (mortality, morbidity, health-related quality of life, dichotomous) – RCT, direct comparison: guselkumab vs. adalimumab, week 48 (research question B, VOYAGE 1) (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: According to the CSR, the outcome was only recorded during the study in patients with psoriasis on the scalp at the start of the study. The proportion of these patients in the subpopulation is unclear; it is about 88% in relation to the total population of the study.
d: According to the CSR, the outcome was only recorded during the study in patients with psoriasis on the hands and feet at the start of the study. The proportion of these patients in the subpopulation is unclear; it is about 30% in relation to the total population of the study.
e: Proportion of the patients for whom the outcome was not recorded is too high.

CI: confidence interval; CSR: clinical study report; DLQI: Dermatology Life Quality Index; hf-PGA: Physician Global Assessment of Hands and/or Feet; n: number of patients with event; N: number of analysed patients; 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 21: Results (morbidity, health-related quality of life, time to event) – RCT, direct comparison: guselkumab vs. adalimumab, week 48 (research question B, VOYAGE 1)

Study Outcome category Outcome	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]
VOYAGE 1					
Morbidity					
PASI					
Remission (PASI 100)	170	4.67 [3.94; 5.65] ND	179	NA [7.39; NC] ND	1.93 [1.45; 2.57]; < 0.001
PASI 90	*170*	*2.79 [2.79; 2.89]* *ND*	*179*	*3.02 [2.79; 3.71]* *ND*	*1.44 [1.12; 1.84]; 0.004*
PASI 75	*170*	*1.87 [1.87; 1.91]* *ND*	*179*	*1.87 [1.87; 2.00]* *ND*	*1.28 [1.01; 1.62]; 0.043*
Patient-reported symptoms (PSSD)					
Symptom score 0	170	NA ND	179	NA ND	1.63 [1.06; 2.49]; 0.025
Sign score 0	170	NA ND	179	NA ND	1.97 [1.24; 3.13]; 0.004
No psoriasis symptoms on the scalp (ss-IGA 0)[b]	170	3.84 [NC; NC] ND	179	5.55 [NC; NC] ND	1.29 [0.98; 1.69]; 0.066
No psoriasis symptoms on hands and feet (hf-PGA 0)[c]	No usable data[d]				
Health-related quality of life					
DLQI (0 or 1)	170	3.78 [3.71; 5.52] ND	179	5.62 [3.94; 11.07] ND	1.57 [1.18; 2.07]; 0.002

a: It is assumed that the calculation of HR, CI and p-value was conducted as follows: Cox proportional hazards model stratified by study centres.
b: According to the CSR, the outcome was only recorded during the study in patients with psoriasis on the scalp at the start of the study. The proportion of these patients in the subpopulation is unclear; it is about 88% in relation to the total population of the study.
c: According to the CSR, the outcome was only recorded during the study in patients with psoriasis on the hands and feet at the start of the study. The proportion of these patients in the subpopulation is unclear; it is about 30% in relation to the total population of the study.
d: Proportion of the patients for whom the outcome was not recorded is too high.

CI: confidence interval; CSR: clinical study report; DLQI: Dermatology Life Quality Index; hf-PGA: Physician Global Assessment of Hands and/or Feet; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; NC: not calculable; ND: no data; 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 22: Results for patients with nail psoriasis at study start (morbidity [NAPSI], dichotomous) – RCT, direct comparison: guselkumab vs. adalimumab, week 48 (research question B, VOYAGE 1)

Study Outcome category	Guselkumab		Adalimumab		Guselkumab vs. adalimumab
Outcome	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value[b]
VOYAGE 1					
Morbidity					
No psoriasis symptoms on the nails					
NAPSI 0[c]	108	49 (45.4[d])	112	56 (50.0[d])	0.91 [0.69; 1.20]; 0.532

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 information on how many patients in the relevant subpopulation were affected at the start of the study was explained by the company during the oral hearing [5].
b: Institute‘s calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [9]).
c: NRI analysis.
d: Institute’s calculation.

CI: confidence interval; n: number of patients with one event; CSR: clinical study report; CSZ: convexity, symmetry, z score; N: number of analysed patients; NAPSI: Nail Psoriasis Severity Index; NRI: non-responder imputation; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 23: Results for patients with nail psoriasis at study start (morbidity [NAPSI], time to event) – RCT, direct comparison: guselkumab vs. adalimumab, week 48 (research question B, VOYAGE 1)

Study Outcome category Outcome	Guselkumab		Adalimumab		Guselkumab vs. adalimumab
	N[a]	Median time to event in months [95% CI] Patients with event n (%)	N[a]	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
VOYAGE 1					
Morbidity					
No psoriasis symptoms on the nails					
NAPSI 0	170	11.11 [11.07; NC] ND	179	11.11 [11.07; 11.24] ND	0.59 [0.38; 0.92]; 0.019

a: According to the CSR, the outcome was only recorded during the study in patients with nail psoriasis at the start of the study (about 63% of the patients). In the company's analysis, the remaining patients were censored at the start of the study [5].
b: It is assumed that the calculation of HR, CI and p-value was conducted as follows: Cox proportional hazards model stratified by study centres.
CI: confidence interval; CSR: clinical study report; HR: hazard ratio; n: number of patients with one event; N: number of analysed patients; NA: not achieved; NAPSI: Nail Psoriasis Severity Index; NC: not calculable; ND: no data; RCT: randomized controlled trial; vs.: versus

Table 24: Results (side effects, dichotomous) – RCT, direct comparison: guselkumab vs. adalimumab, week 48 (research question B, VOYAGE 1)

Study Outcome category Outcome	Guselkumab		Adalimumab		Guselkumab vs. adalimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
VOYAGE 1					
Side effects					
AEs (supplementary information)	170	136 (80.0)	178	131 (73.6)	–
SAEs	170	7 (4.1)	178	8 (4.5)	0.92 [0.34; 2.47]; > 0.999
Discontinuation due to AEs	170	1 (0.6)	178	7 (3.9)	0.15 [0.02; 1.20]; 0.068
Infections and infestations	170	96 (56.5)	178	85 (47.8)	1.18 [0.97; 1.45]; 0.109

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; SAE: serious adverse event; vs.: versus

B.2 – Kaplan-Meier curves

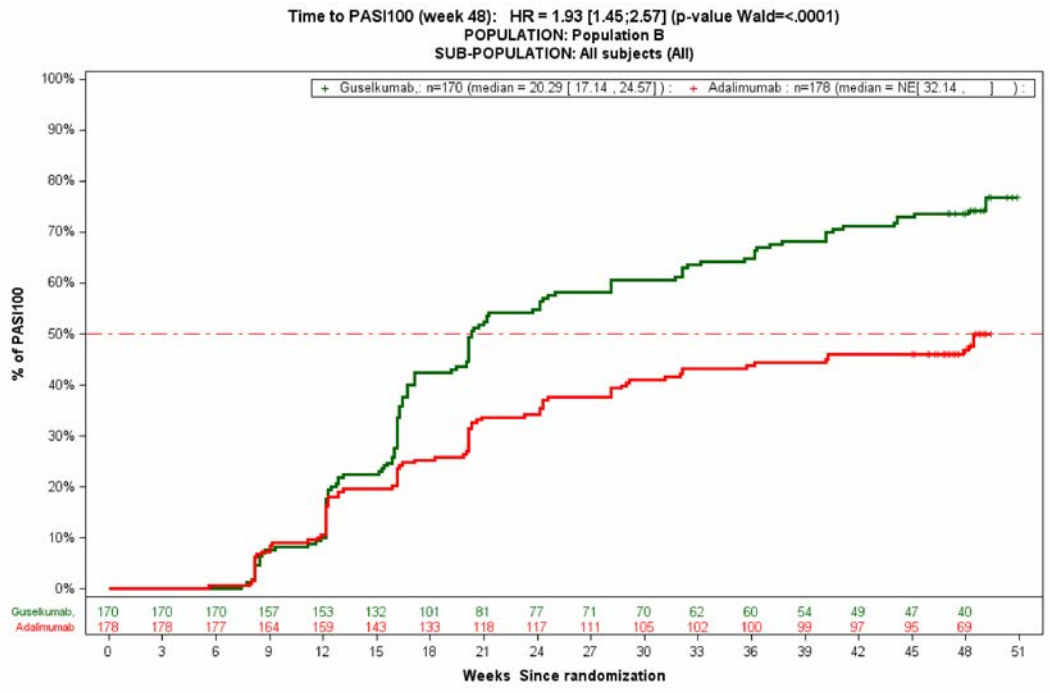

Figure 5: Kaplan-Meier curve for the outcome "PASI 100" from the VOYAGE 1 study until week 48

B.3 – Results for the outcome "hf-PGA 0"

Table 25: Results for patients with psoriasis on hands and feet at study start (morbidity [hf-PGA 0], dichotomous) – RCT, direct comparison: guselkumab vs. adalimumab, week 48 (research question B, VOYAGE 1)

Study Outcome category Outcome	Guselkumab		Adalimumab		Guselkumab vs. adalimumab
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value[b]
VOYAGE 1					
Morbidity					
No psoriasis symptoms on hands and feet (hf-PGA 0)[c]	170	40 (23.5)	179	29 (16.2)	1.38 [0.94; 2.04]; 0.102

a: According to the CSR, the outcome was only recorded during the study in patients with psoriasis on the hands and feet at the start of the study. The proportion of these patients in the subpopulation is unclear; it is about 28% in relation to the total population of the studies.
b: RR, 95% CI and p-value were determined with the Cochran-Mantel-Haenszel method under consideration of the stratification according to study centres.
c: NRI analysis.
CI: confidence interval; CSR: clinical study report; hf-PGA: Physician Global Assessment of Hands and/or Feet; n: number of patients with event; N: number of analysed patients; NRI: non-responder imputation; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 26: Results for patients with psoriasis on hands and feet at study start (morbidity [hf-PGA 0], time to event) – RCT, direct comparison: guselkumab vs. adalimumab, week 48 (research question B, VOYAGE 1)

Study Outcome category Outcome	Guselkumab		Adalimumab		Guselkumab vs. adalimumab
	N[a]	Median time to event in months [95% CI] Patients with event n (%)	N[a]	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
VOYAGE 1					
Morbidity					
No psoriasis symptoms on hands and feet (hf-PGA 0)	170	3.71 [3.71; 3.94] ND	179	5.59 [3.78; 10.84] ND	1.71 [0.93; 3.12]; 0.082

a: According to the CSR, the outcome was only recorded during the study in patients with psoriasis on the hands and feet at the start of the study. The proportion of these patients in the subpopulation is unclear; it is about 30% in relation to the total population of the study. According to statements by the company in the oral hearing, the remaining patients were censored at the start of the study [5].
b: It is assumed that the calculation of HR, CI and p-value was conducted as follows: Cox proportional hazards model stratified by study centres.

CI: confidence interval; CSR: clinical study report; hf-PGA: Physician Global Assessment of Hands and/or Feet; HR: hazard ratio; N: number of analysed patients; n: patients with event; ND: no data; RCT: randomized controlled trial; vs.: versus