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(Addendum to Commission A15-20)[1]

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Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CI	confidence interval
DLQI	Dermatology Life Quality Index
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PASI	Psoriasis Area and Severity Index
PUVA	psoralen and ultraviolet-A light
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
VAS	visual analogue scale

1 Background

On 9 October 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A15-20 (Secukinumab – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In its comment [2], the pharmaceutical company (hereinafter referred to as "the company") submitted supplementary information, which went beyond the information provided in the dossier, to prove the added benefit [3]. These were new analyses on the outcomes already presented in the dossier and analyses on one new time point (52 weeks) of the relevant study CAIN 457A2317 (CLEAR) on the comparison of secukinumab and ustekinumab. The G-BA therefore commissioned IQWiG with the assessment of the analyses on the 52-week data of the CLEAR study for subpopulation B submitted by the company in the commenting procedure under consideration of the information provided in the dossier.

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

2 Assessment

The documents subsequently submitted by the company in the commenting procedure, which are hereinafter assessed, exclusively refer to research question B of dossier assessment A15-20, i.e. to the therapeutic indication of patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA), or with contraindication or intolerance to such treatments.

No new data were available for the population of patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy so that the conclusion on extent and probability of the added benefit drawn in dossier assessment A15-20 for this patient group remains unchanged (see also Section 2.3.3).

2.1 Documents subsequently submitted

The CAIN 457A2317 study on the comparison of secukinumab and ustekinumab presented by the company was included in the dossier assessment. However, the dossier only contained analyses from an interim analysis at week 24 of the 52-week study. Since not all outcomes were recorded also at week 24, only analyses at an earlier time point were available for some of the outcomes, particularly on health-related quality of life. Due to the minimum study duration of 24 weeks required for the benefit assessment, the results on these outcomes available in the dossier were not evaluable.

For the outcomes for which an improvement of symptoms was measured using the Psoriasis Area and Severity Index (PASI), the company presented analyses on different threshold values in the dossier, i.e. on the 75% improvement (PASI 75), on the 90% improvement (PASI 90) and on the 100% improvement (PASI 100). For these outcomes, the dossier contained analyses on the proportion of patients with the respective improvement at week 24. Due to the uncertainty regarding the interpretability of a certain improvement in PASI, only the results on the PASI 100 were considered in the dossier assessment. With the comment, the company also submitted analyses on the time to first achieving the respective threshold value as supplementation to the analyses on the proportion of patients with achievement of a certain threshold value presented in the dossier. These were also considered relevant for the benefit assessment.

In addition, the company presented analyses at week 52 of the CAIN 457A2317 study for all relevant outcomes during the hearing. Since plaque psoriasis is a chronic disease, data from an observation period that is as long as possible are preferred. For this reason, hereinafter only the results at week 52 of the CAIN 457A2317 study are considered.

In the following Sections 2.2 and 2.3, the 52-week data of the CAIN 457A2317 study are assessed on the basis of the outcomes included in the dossier assessment. Information on the

study characteristics and on the characteristics of the patients included is provided in dossier assessment A15-20.

The results on the outcomes "PASI 75" and "PASI 90", each also at week 52, as well as an explanation of the possible effects of these outcomes on the overall conclusion on extent and probability of the added benefit of secukinumab for research question B are presented in Section 2.4.

2.2 Results on added benefit

2.2.1 Outcomes included

The choice of outcomes can be found in dossier assessment A15-20 [1].

Table 1 shows for which outcomes data were available in the study included.

Table 1: Matrix of outcomes – RCT, direct comparison: secukinumab vs. ustekinumab

Study	Outcomes										
	All-cause mortality	Remission (PASI 100, event rate)[a]	Remission (PASI 100, time to first event)[b]	Symptoms (pain)[c]	Symptoms (itching)[c]	Symptoms (scaling)[c]	Health status (EQ-5D VAS)	Health-related quality of life (DLQI responder[d])	SAEs	Discontinuation due to AEs	Infections and infestations
CAIN457A2317	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: Improvement on PASI score by 100% at week 52 compared with baseline.
b: Time to first improvement by 100% compared with baseline within 52 weeks.
c: Recorded on a numerical scale (0–10).
d: A score of 0 or 1 at week 52 was assessed as DLQI response.

AE: adverse event; DLQI: Dermatology Life Quality Index; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

2.2.2 Risk of bias

Table 2 shows the risk of bias for the relevant outcomes.

Table 2: Risk of bias at study and outcome level – RCT, direct comparison: secukinumab vs. ustekinumab

Study	Study level	Outcomes										
		All-cause mortality	Remission (PASI 100, event rate)[a]	Remission (PASI 100, time to first event)[b]	Symptoms (pain)[c]	Symptoms (itching)[c]	Symptoms (scaling)[c]	Health status (EQ-5D VAS)	Health-related quality of life (DLQI responder)[d]	SAEs	Discontinuation due to AEs	Infections and infestations
CAIN457A2317	L	L	L	L	L	L	L	L	L	L	L	L

a: Improvement on PASI score by 100% at week 52 compared with baseline.
b: Time to first improvement by 100% compared with baseline within 52 weeks.
c: Recorded on a numerical scale (0–10).
d: A score of 0 or 1 at week 52 was assessed as DLQI response.

AE: adverse event; DLQI: Dermatology Life Quality Index; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; L: low; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The risk of bias at the study level was rated as low, which concurs with dossier assessment A15-20. The risk of bias at outcome level was also rated as low for all relevant outcomes.

2.2.3 Results

Table 3 to Table 5 present the results of the comparison of secukinumab with ustekinumab in patients with plaque psoriasis with inadequate response to other systemic treatments or who are unsuitable for these treatments. The data subsequently submitted in the company's comment were, where necessary, supplemented by the Institute's calculations. Kaplan-Meier curves on the survival time analysis of the PASI 100 can be found in Appendix A.

Table 3: Results (dichotomous outcomes, week 52) – RCT, direct comparison: secukinumab vs. ustekinumab

Study Outcome category Outcome	Secukinumab		Ustekinumab		Secukinumab vs. ustekinumab
	N^a	Patients with event n (%)	N^a	Patients with event n (%)	RR [95% CI]; p-value
CAIN 457A2317					
Mortality					
All-cause mortality	163	0 (0)	148	1 (0.7)	0.30 [0.01; 7.38]; 0.361[b]
Morbidity					
Remission (PASI 100)[c]	163	59 (36.2)	148	39 (26.4)	1.37 [0.98; 1.93]; 0.063[b]
Health-related quality of life					
DLQI responder[d]	162	100 (61.7)	148	73 (49.3)	1.25 [1.02; 1.53]; 0.029[b]
Adverse events					
AEs (supplementary information)	163	147 (90.2)	148	127 (85.8)	–
SAEs	163	13 (8.0)	148	12 (8.1)	0.98 [0.46; 2.09]; > 0.999[b]
Discontinuation due to AEs	163	6 (3.7)	148	5 (3.4)	1.09 [0.34; 3.50]; 0.922[b]
Infections and infestations	163	99 (60.7)	148	94 (63.5)	0.96 [0.80; 1.14]; 0.648[b]

a: Results of the FAS population for which one value at baseline and at least one value in the course of the study were available.
b: Institute's calculation, unconditional exact test (CSZ method according to [4]).
c: Improvement on PASI score by 100% at week 52 compared with baseline.
d: A score of 0 or 1 at week 52 was considered DLQI response; LOCF analysis of the FAS population for which one value at baseline and at least one value in the course of the study were available.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; DLQI: Dermatology Life Quality Index; FAS: full analysis set; N: number of analysed patients; n: number of patients with event; NC: not calculable; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 4: Results (outcome "PASI 100", time to first event until week 52) – RCT, direct comparison: secukinumab vs. ustekinumab

Study Outcome category Outcome	Secukinumab		Ustekinumab		Secukinumab vs. ustekinumab
	N[a]	Median time to first achievement of PASI 100/ Kaplan-Meier estimator[b] % (SE)[c]	N[a]	Median time to first achievement of PASI 100/ Kaplan-Meier estimator[b] % (SE)[c]	HR [95% CI]; p-value[c]
CAIN 457A2317					
Morbidity					
Remission (PASI 100)[d]	164	ND/ 69.74 (3.68)	149	ND/ 55.26 (4.19)	1.52 [1.14; 2.02]; 0.005

a: Results of the FAS population.
b: Kaplan-Meier estimator at week 52; indicates the cumulative proportion of the patients who had achieved remission in the course of the study.
c: Cox regression with treatment, adjusted for baseline PASI score and by weight (≤ 100 kg, > 100 kg).
d: Operationalized as time to first improvement by 100% compared with baseline within 52 weeks.
CI: confidence interval; FAS: full analysis set; HR: hazard ratio; N: number of analysed patients; ND: no data; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; SE: standard error; vs.: versus

Table 5: Results (continuous outcomes, week 52) – RCT, direct comparison: secukinumab vs. ustekinumab

Study Outcome category Outcome	Secukinumab			Ustekinumab			Secukinumab vs. ustekinumab
	N[a]	Baseline values mean (SE)	Change at week 52 mean[b,c] (SE)	N[a]	Baseline values mean (SE)	Change at week 52 mean[b,c] (SE)	MD [95% CI][c]; p-value
CAIN 457A2317							
Morbidity							
Symptoms[d]							
Pain	162	5.17 (0.24)	−4.04 (0.18)	148	5.09 (0.24)	−3.73 (0.19)	−0.31 [−0.78; 0.16]; 0.196
Itching	162	7.43 (0.17)	−5.79 (0.20)	148	7.29 (0.17)	−5.20 (0.21)	−0.58 [−1.11; −0.06]; 0.030 Hedges' g: −0.23 [−0.45; −0.01][e]
Scaling	162	7.64 (0.18)	−6.34 (0.18)	148	7.55 (0.17)	−5.60 (0.19)	−0.74 [−1.22; −0.27]; 0.002 Hedges' g: −0.32 [−0.55; −0.10][e]
Health status							
EQ-5D VAS[f]	162	64.75 (1.78)	17.60 (1.53)	148	65.20 (1.95)	15.58 (1.61)	2.01 [−1.97; 6.00]; 0.321

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: Unless stated otherwise, LOCF analysis of the FAS population for which one value at baseline and at least one value in the course of the study were available.
c: Model adjusted by treatment, weight (≤ 100 kg, > 100 kg) and the respective baseline value.
d: Negative changes indicate improvement of symptoms on a 0–10 scale.
e: Institute's calculation; approximation of the pooled standard deviation for Hedges' g using the standard errors shown and the patient numbers.
f: Positive changes indicate improvement.
CI: confidence interval; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; FAS: full analysis set; LOCF: last observation carried forward; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SE: standard error; vs.: versus

Mortality

All-cause mortality

In total, one death occurred in the ustekinumab group in the CAIN 457A2317 study until treatment week 52. The difference between the treatment groups was not statistically significant. Hence there was no hint of an added benefit of secukinumab in comparison with ustekinumab; an added benefit is therefore not proven.

Morbidity

Remission (PASI 100)

There were 2 operationalizations for the outcome "remission" (measured with the PASI 100): one was the proportion of patients in remission at the time point of week 52 (hereinafter referred to as "proportion of events"), and the other was the time to first achieving remission during the course of the study of 52 weeks. Regarding the proportion of patients with a PASI 100 at the time point of week 52, no statistically significant difference between the treatment groups was shown in the CAIN 457A2317 study. For the time to first achieving the PASI 100, a statistically significant difference in favour of secukinumab was shown, however.

The proportions of events and the Kaplan-Meier estimators at week 52 are to be considered per treatment group in the interpretation of the results. Whereas the proportions of events show how many patients were under remission exactly at the time point of 52 weeks, the Kaplan-Meier estimator indicates the entire (cumulative) proportion of all patients who had remission at any time during the course of the study. Table 3 and Table 4 show that the proportions of events at week 52 (secukinumab: 36%, ustekinumab: 26%) were considerably lower than the Kaplan-Meier estimators at the same time point (secukinumab: 70%, ustekinumab: 55%). It can be concluded that the symptoms recurred in a large proportion of the patients. Hence conclusions regarding the duration of a remission would be necessary for a robust assessment in order to eventually gain knowledge about the actual burden of symptoms over the total time period of 52 weeks. Neither the analyses on the proportion of patients with remission at a certain time point nor the time to first achieving remission allow conclusions on the durability of the remission, however. This would require analyses that also consider the duration of the remission. Due to the same direction of the effect of all available operationalizations (also those at week 24 [see dossier assessment A15-20]) it is not assumed overall that there is no effect of secukinumab in comparison with ustekinumab regarding remission. It is unclear, however, whether the effect in this outcome of the category "non-serious/non-severe symptoms/late complications" is so large overall that its extent is more than marginal. The results are therefore subject to increased uncertainty.

In summary, there is a hint of an added benefit of secukinumab in comparison with ustekinumab regarding remission.

Symptoms: pain

No statistically significant difference between the treatment groups was shown for the outcome "pain". However, there was proof of an effect modification by the characteristic "previous treatment with biologics".

For patients with previous treatment with biologics, there was an indication of an added benefit of secukinumab in comparison with ustekinumab. For patients without previous

treatment with biologics, however, there was no hint of an added benefit of secukinumab in comparison with ustekinumab; an added benefit for these patients is therefore not proven.

Symptoms: itching

A statistically significant difference in favour of secukinumab was shown for the outcome "itching". However, the 95% confidence interval (CI) of the standardized mean difference (SMD) did not lie completely below the irrelevance threshold of −0.2. It can therefore not be inferred that the effect is relevant. Furthermore, there was proof of an effect modification by the characteristic "previous treatment with biologics".

For patients with previous treatment with biologics, there was an indication of an added benefit of secukinumab in comparison with ustekinumab. For patients without previous treatment with biologics, however, there was no hint of an added benefit in comparison with ustekinumab; an added benefit for these patients is therefore not proven.

Symptoms: scaling

A statistically significant difference in favour of secukinumab was shown for the outcome "scaling". However, the 95% CI of the SMD did not lie completely below the irrelevance threshold of −0.2. It can therefore not be inferred that the effect is relevant. Furthermore, there was proof of an effect modification by the characteristic "previous treatment with biologics".

For patients with previous treatment with biologics, there was an indication of an added benefit of secukinumab in comparison with ustekinumab. For patients without previous treatment with biologics, however, there was no hint of an added benefit in comparison with ustekinumab; an added benefit for these patients is therefore not proven.

Health status (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS])

There was no statistically significant difference between the treatment groups for the outcome "health status (EQ-5D VAS)". Hence there was no hint of an added benefit of secukinumab in comparison with ustekinumab; an added benefit is therefore not proven.

Health-related quality of life

DLQI responder

Regarding the proportion of patients with a Dermatology Life Quality Index (DLQI) score of 0 or 1 at week 52, a statistically significant difference in favour of secukinumab was shown in the CAIN 457A2317 study. Hence there was an indication of an added benefit of secukinumab in comparison with ustekinumab regarding health-related quality of life.

Adverse events

Serious adverse events, discontinuation due to adverse events as well as infections and infestations

No statistically significant difference between the treatment groups was shown in the CAIN 457A2317 study for any of the outcomes "serious adverse events (SAEs)", "discontinuation due to adverse events (AEs)" and "infections and infestations". Hence there was no hint of greater or lesser harm of secukinumab in comparison with ustekinumab. Greater or lesser harm is therefore not proven.

2.2.4 Subgroups and effect modifiers

As described in dossier assessment A15-20, the following subgroup characteristics were included in the assessment [1]:

- age

- sex

- disease severity

- pretreatment with biologics

- region

The methods for handling results from subgroup analyses are also described in dossier assessment A15-20 [1]. Deviating from this, only those subgroup analyses are considered hereinafter for which a statistically significant and relevant effect was shown in at least one subgroup.

Table 6 shows the results of these subgroup analyses.

Table 6: Subgroups (symptoms: pain, week 52) – RCT, direct comparison: secukinumab vs. ustekinumab

Study Outcome Characteristic Subgroup	Secukinumab			Ustekinumab			Secukinumab vs. ustekinumab
	N[a]	Baseline values mean (SE)	Change at end of study mean[b,c] (SE)	N[a]	Baseline values mean (SE)	Change at end of study mean[b,c] (SE)	MD [95% CI][c]; p-value
CAIN 457A2317							
Symptoms: pain[d]							
Previous treatment with biologics							
Yes	31	5.97 (0.51)	−3.96 (0.37)	21	6.24 (0.63)	−2.19 (0.45)	−1.77 [−2.91; −0.63]; 0.002
							Hedges' g: −0.85 [−1.43; −0.27][e]
No	131	4.98 (0.27)	−4.09 (0.20)	127	4.91 (0.26)	−4.02 (0.20)	−0.07 [−0.57; 0.43]; 0.788
						Interaction:	p-value = 0.008[c]
Symptoms: itching[d]							
Previous treatment with biologics							
Yes	31	7.58 (0.40)	−5.59 (0.41)	21	7.90 (0.41)	−3.24 (0.50)	−2.35 [−3.62; −1.08]; < 0.001
							Hedges' g: −1.01 [−1.60; −0.42][e]
No	131	7.39 (0.19)	−5.88 (0.22)	127	7.19 (0.19)	−5.59 (0.22)	−0.30 [−0.86; 0.26]; 0.296
						Interaction:	p-value = 0.004[c]
Symptoms: scaling[d]							
Previous treatment with biologics							
Yes	31	8.06 (0.35)	−6.09 (0.38)	21	8.14 (0.38)	−4.21 (0.46)	−1.88 [−3.04; −0.71]; 0.002
							Hedges' g: −0.88 [−1.46; −0.30][e]
No	131	7.53 (0.20)	−6.44 (0.20)	127	7.46 (0.19)	−5.87 (0.21)	−0.57 [−1.09; −0.06]; 0.029
							Hedges' g: −0.24 [−0.49; 0.00][e]
						Interaction:	p-value = 0.045[c]

(continued)

Table 6: Subgroups (symptoms: pain, week 52) – RCT, direct comparison: secukinumab vs. ustekinumab (continued)

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: Unless stated otherwise, LOCF analysis of the FAS population for which one value at baseline and at least one value in the course of the study were available. c: Model adjusted by treatment, weight ($\leq$ 100 kg, > 100 kg) and the respective baseline value. d: Negative changes indicate improvement of symptoms on a 0–10 scale. e: Institute's calculation; approximation of the pooled standard deviation for Hedges' g using the standard errors shown and the patient numbers. CI: confidence interval; FAS: full analysis set; LOCF: last observation carried forward; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SE: standard error; vs.: versus

Morbidity

Symptoms: pain, itching, scaling

There was proof of an effect modification by the characteristic "previous treatment with biologics" for each of the outcomes "pain", "itching" and "scaling".

A statistically significant difference in favour of secukinumab was shown in each case for patients with previous treatment with biologics. In each case, the 95% CI of Hedges' g was completely below the irrelevance threshold of −0.2. This was interpreted to be a relevant effect. Hence there was an indication of an added benefit of secukinumab in comparison with ustekinumab regarding the outcomes "pain", "itching" and "scaling".

No statistically significant difference between the treatment groups was shown for patients without previous treatment with biologics for each of the outcomes "pain" and "itching". Hence in each case, there was no added benefit of secukinumab in comparison with ustekinumab in these patients; an added benefit is therefore not proven. A statistically significant difference in favour of secukinumab was shown for the outcome "scaling". The 95% CI of Hedges' g was not completely below the irrelevance threshold of −0.2. It can therefore not be inferred that the effect is relevant. Hence there was no hint of an added benefit also regarding the outcome "scaling" in these patients; an added benefit is therefore not proven.

2.3   Extent and probability of added benefit

The derivation of extent and probability of 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 [5].

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.

2.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.2.3 resulted in indications or hints of an added benefit for several outcomes, in some cases only for individual subgroups. The extent of the respective added benefit at outcome level was estimated from these results (see Table 7).

Table 7: Extent of added benefit at outcome level: secukinumab vs. ustekinumab

Outcome category **Outcome** **Operationalization or effect modifier** **Subgroup**	**Secukinumab vs. ustekinumab** **Proportion of events or MD** **Effect estimates [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Deaths	0% vs. 0.7% RR: 0.30 [0.01; 7.38]; p = 0.361	Added benefit not proven
Morbidity		
Remission (PASI 100)		
Proportion of patients with PASI 100	36% vs. 26% RR: 1.37 [0.98; 1.93] p = 0.063	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Time to first achievement of PASI 100	KM estimator 70% vs. 55% HR: 1.52 [1.14; 2.02] HR: 0.66 [0.50; 0.88][c] p = 0.005	
	Summarizing assessment: probability: "hint"	
Pain		
Previous treatment with biologics		
Yes	−3.96 vs. −2.19 MD: −1.77 [−2.91; −0.63] SMD: −0.85 [−1.43; −0.27][d] p = 0.002 probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
No	−4.09 vs. −4.02 MD: −0.07 [−0.57; 0.43] p = 0.788	Added benefit not proven
Itching		
Previous treatment with biologics		
Yes	−5.59 vs. −3.24 MD: −2.35 [−3.62; −1.08] SMD: −1.01 [−1.60; −0.42][d] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
No	−5.88 vs. −5.59 MD: −0.30 [−0.86; 0.26] p = 0.296	Added benefit not proven

(continued)

Table 7: Extent of added benefit at outcome level: secukinumab vs. ustekinumab (continued)

Outcome category
Outcome
  Effect modifier
    Subgroup
	Secukinumab vs. ustekinumab
	Proportion of events or MD
	Effect estimates [95% CI]; p-value
	Probability[a]
		Derivation of extent[b]

Scaling		
Previous treatment with biologics		
Yes	−6.09 vs. −4.21 MD: −1.88 [−3.04; −0.71] SMD: −0.88 [−1.46; −0.30][d] p = 0.002 probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
No	−6.44 vs. −5.87 MD: −0.57 [−1.09; −0.06] SMD: -0.24 [−0.49; 0.00][d] p = 0.029	Added benefit not proven
Health status	17.60 vs. 15.58 MD: 2.01 [−1.97; 6.00] p = 0.321	Added benefit not proven
Health-related quality of life		
DLQI responder	62% vs. 49% RR: 1.25 [1.02; 1.53] RR: 0.80 [0.65; 0.98][c] p = 0.029 probability: "indication"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Adverse events		
SAEs	8% vs. 8% RR: 0.98 [0.46; 2.09] p > 0.999	Greater/lesser harm not proven
Discontinuation due to AEs	4% vs. 3% RR: 1.09 [0.34; 3.50] p = 0.992	Greater/lesser harm not proven
Infections and infestations	61% vs. 64% RR: 0.96 [0.80; 1.14] p = 0.648	Greater/lesser harm not proven
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: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit. d: Added benefit assumed with upper and lower CI limits < −0.2 and > 0.2. AE: adverse event; CI: confidence interval; CI_u: upper limit of the CI; DLQI: Dermatology Life Quality Index; KM: Kaplan-Meier; MD: mean difference; PASI: Psoriasis Area and Severity Index; RR: relative risk; SAE: serious adverse event; SMD: standardized mean difference; vs.: versus		

2.3.2 Overall conclusion on added benefit

Table 8 summarizes the results that were considered in the overall conclusion on the extent of added benefit for patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including cyclosporine, methotrexate or PUVA, or with contraindication or intolerance to such treatments.

Table 8: Positive and negative effects from the assessment of secukinumab in comparison with ustekinumab

Positive effects	Negative effects
Hint of added benefit – extent: "minor" (non-serious/non-severe symptoms/late complications: remission [PASI 100])	–
Patients with previous treatment with biologics: indication of added benefit – extent "non-quantifiable" (non-serious /non-severe symptoms/late complications: pain)	
Patients with previous treatment with biologics: indication of added benefit – extent "non-quantifiable" (non-serious /non-severe symptoms/late complications: itching)	
Patients with previous treatment with biologics: indication of added benefit – extent "non-quantifiable" (non-serious /non-severe symptoms/late complications: scaling)	
Indication of added benefit – extent: "minor" (health-related quality of life: DLQI responder)	
DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index	

Overall only positive effects remain in the outcome categories "non-serious/non-severe symptoms/late complications" and "health-related quality of life", in each case with the same probability (indication), but partly only for the subgroup of patients with previous treatment with biologics.

There is an indication of a minor added benefit for the outcome category "health-related quality of life (DLQI)". Furthermore, there is a hint of a minor added benefit for the outcome category "non-serious/non-severe symptoms/late complications". In addition, there is an indication of a non-quantifiable added benefit in 3 outcomes of the outcome category "non-serious/non-severe symptoms/late complications" for patients with previous treatment with biologics. No sufficient information was available for these outcomes to categorize the extent as "minor" or "considerable".

As a result, there are separate conclusions on the added benefit for patients with and without previous treatment with biologics within the patients with moderate to severe plaque psoriasis

with inadequate response to other systemic treatments including cyclosporine, methotrexate or PUVA, or with contraindication or intolerance to such treatments.

In summary, there is an indication of a non-quantifiable added benefit for patients with previous treatment with biologics. There is an indication of a minor added benefit for those patients who have not been pretreated with biologics.

2.3.3 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of secukinumab in comparison with the ACT is summarized in Table 9.

Table 9: Secukinumab – extent and probability of added benefit

Research question	Therapeutic indication	ACT[a]	Subgroup	Extent and probability of added benefit
A	Adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy[b]	Individually optimized standard treatment under consideration of fumaric acid esters or cyclosporine or methotrexate[c] or phototherapy (balneo-phototherapy, oral PUVA, NB-UVB)	–	Added benefit not proven
B	Adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including cyclosporine, methotrexate or PUVA, or with contraindication or intolerance to such treatments	Adalimumab or infliximab or **ustekinumab**	Patients with previous treatment with biologics	Indication of a non-quantifiable added benefit
			Patients without previous treatment with biologics	Indication of minor 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: This population includes all patients in the approved therapeutic indication less the patients named in research question B.				
c: The company chose methotrexate as only comparator therapy. This approach was not followed.				
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B; PUVA: psoralen and ultraviolet-A light				

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

2.4 Presentation of the results on the outcomes on response (PASI 75 and PASI 90)

Hereinafter, the results on the outcomes on response (PASI 75 and PASI 90) from the CAIN 457A2317 study are presented for patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including cyclosporine, methotrexate or PUVA, or with contraindication or intolerance to such treatments.

Table 10 shows the results on the proportion of patients who had achieved a PASI 75 or a PASI 90 at the time point week 52; Table 11 shows the results on the time to first achievement of the PASI 75 and of the PASI 90 during the course of the study within 52 weeks. Kaplan-Meier curves on the survival time analyses can be found in Appendix A.

Table 10: Results on PASI 75 and PASI 90 (dichotomous outcomes, week 52) – RCT, direct comparison: secukinumab vs. ustekinumab

Study Outcome category Outcome	Secukinumab		Ustekinumab		Secukinumab vs. ustekinumab
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value
CAIN 457A2317					
Morbidity					
Response (PASI 75)[c]	163	136 (83.4)	148	100 (67.6)	1.23 [1.08; 1.41]; 0.001[b]
Response (PASI 90)[c]	163	110 (67.5)	148	78 (52.7)	1.28 [1.06; 1.54]; 0.008[b]
a: Results of the FAS population for which one value at baseline and at least one value in the course of the study were available. b: Institute's calculation, unconditional exact test (CSZ method according to [4]). c: Improvement on PASI score by at least 75% or 90% at week 52 compared with baseline. CI: confidence interval; FAS: full analysis set; N: number of analysed patients; n: number of patients with event; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; vs.: versus					

Table 11: Results (outcome "PASI", time to first event until week 52) – RCT, direct comparison: secukinumab vs. ustekinumab

Study Outcome category	Secukinumab		Ustekinumab		Secukinumab vs. ustekinumab
Outcome	N[a]	Median time to first achievement of response/ Kaplan-Meier estimator[b] % (SE)[c]	N[a]	Median time to first achievement of response/ Kaplan-Meier estimator[b] % (SE)[c]	HR [95% CI]; p-value[c]
CAIN 457A2317					
Response (PASI 75)[d]	164	ND 96.79 (1.45)	149	ND 95.24 (1.88)	1.39 [1.11; 1.76]; 0.005
Response (PASI 90)[d]	164	ND 89.93 (2.46)	149	ND 88.00 (2.77)	1.46 [1.14; 1.86]; 0.002

a: Results of the FAS population.
b: Kaplan-Meier estimator at week 52; indicates the cumulative proportion of the patients who had achieved response in the course of the study.
c: Cox regression with treatment, adjusted for baseline PASI score and by weight (≤ 100 kg, > 100 kg).
c: Operationalized as time to first improvement by at least 75% or 90% compared with baseline within 52 weeks.
CI: confidence interval; FAS: full analysis set; HR: hazard ratio; N: number of analysed patients; ND: no data; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; SE: standard error; vs.: versus

Possible effects of the results on the overall conclusion on the added benefit

For both threshold values (PASI 75 and PASI 90), a statistically significant difference in favour of secukinumab was shown both regarding the proportion of patients with response and regarding the time to first achieving the response.

The results on response (PASI 75 and PASI 90) are largely consistent with the ones on remission (PASI 100) (see Table 3 and Table 4), particularly regarding the time to first achieving response or remission. In the consideration of the period until week 52, a statistically significant difference in favour of secukinumab was shown for all 3 threshold values (PASI 75, PASI 90 and PASI 100). The upper limits of the 95% CI (with reversed direction of effect) were about 0.90, 0.88 and 0.88 and thus close to one another for the threshold values PASI 75, PASI 90 and PASI 100. This shows that the results do not differ to a relevant degree also regarding their extent; the effect size for the PASI 75, in contrast to the PASI 100, is possibly even only marginal. In addition, regarding the proportion of patients with response at the time point week 52, the effect was marginal both for the PASI 75 and for the PASI 90 (upper limit of the 95%-CI with reversed direction of effect 0.93 [PASI 75] and 0.94 [PASI 90]). The explanations in Section 2.2.3 on the durability of the remission applies to the outcomes on response (PASI 75 and PASI 90) to the same extent.

Overall, the additional consideration of the outcomes PASI 75 and PASI 90 in the present benefit assessment provided no additional information regarding extent and probability of the

added benefit of secukinumab in comparison with ustekinumab in patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including cyclosporine, methotrexate or PUVA, or with contraindication or intolerance to such treatments.

3 References

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Appendix A– Figures on survival time analyses (Kaplan-Meier curves)
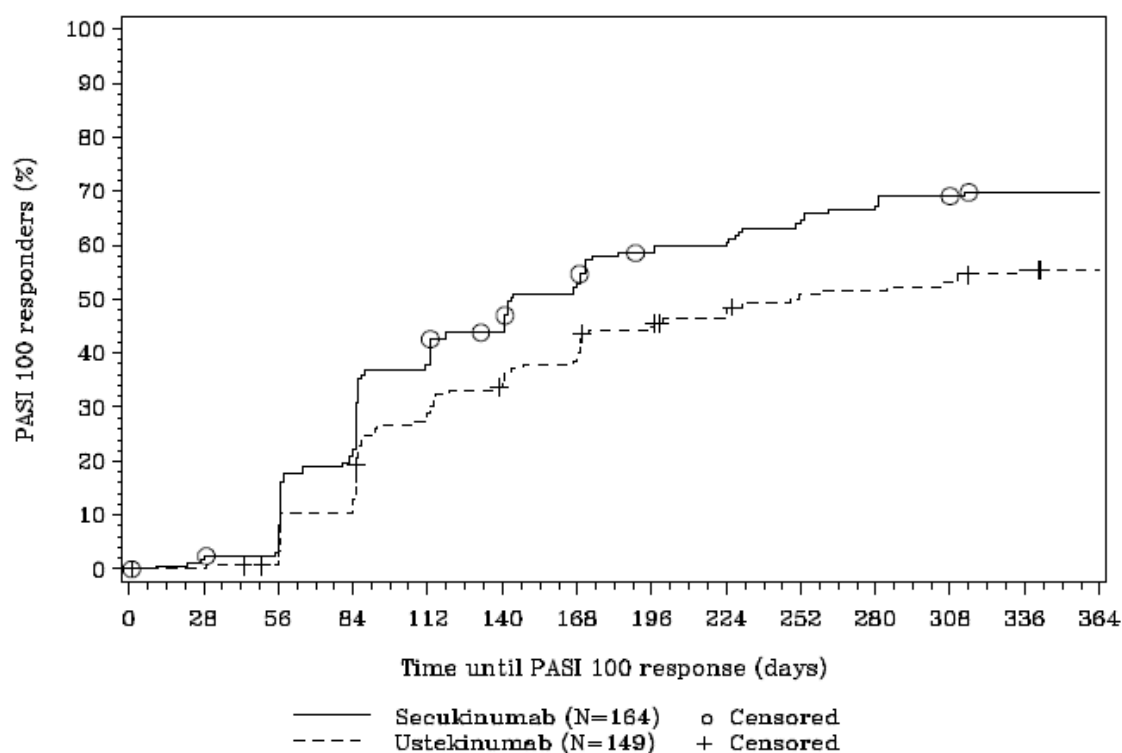
Patients at risk (Secukinumab/Ustekinumab): Day 0: 164/149, Day 28: 159/148, Day 56: 149/141, Day 84: 126/127, Day 112: 101/103, Day 140: 89/94, Day 168: 74/86, Day 196: 63/77, Day 224: 60/70, Day 252: 54/66, Day 280: 50/65, Day 308: 46/63, Day 336: 44/59, Day 364: 44/57
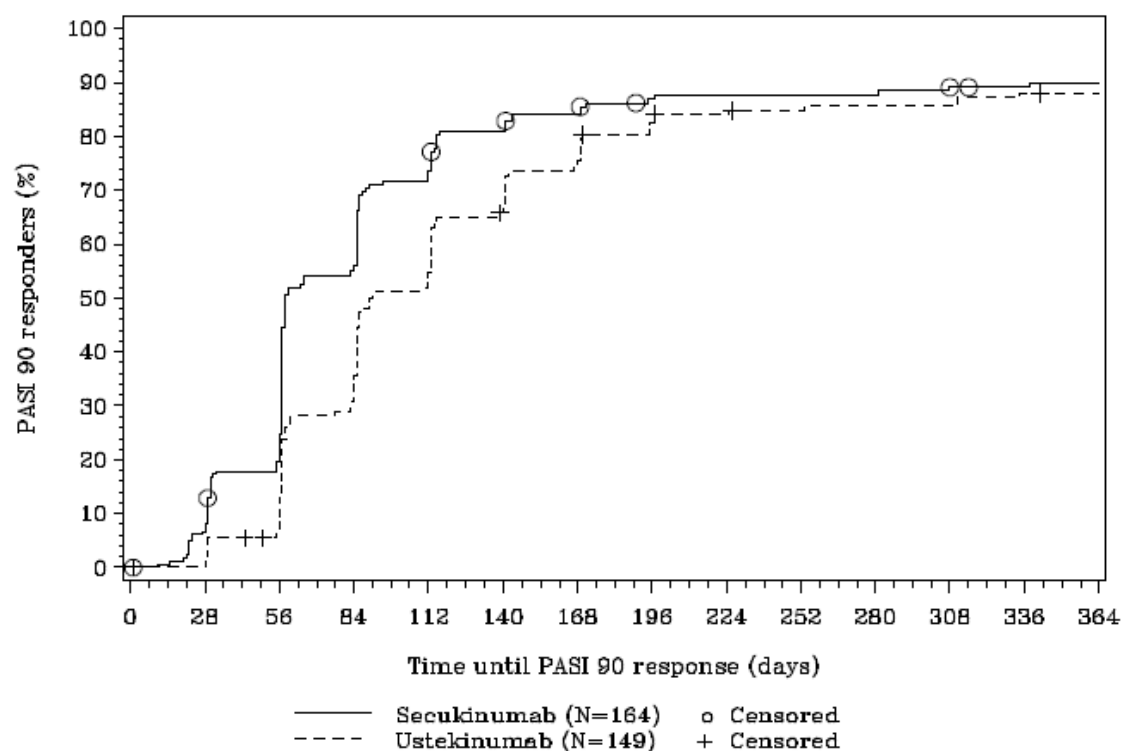
Logrank test: p-value = 0,007 **
**: p < 0,05; *: p < 0,1

Censoring occurs one day after the last regular visit. Discontinued patients are censored at day of discontinuation. Patients without any response assessment are censored at day 1

Analysis population: A2317 FAS subpopulation B (Patients with ((PASI > 10 or BSA > 10) and DL-QI > 10) and lack of efficacy or lack of tolerability or contraindication to at least 1 conventional systemic psoriasis treatment)

Figure 1: Kaplan-Meier curves for the time to first achieving PASI 100 remission – RCT, direct comparison: secukinumab vs. ustekinumab

Patients at risk (Secukinumab/Ustekinumab): Day 0: 164/149, Day 28: 150/146, Day 56: 122/126, Day 84: 71/94, Day 112: 43/66, Day 140: 30/47, Day 168: 24/35, Day 196: 18/24, Day 224: 17/21, Day 252: 17/19, Day 280: 17/18, Day 308: 14/18, Day 336: 13/15, Day 364: 12/14
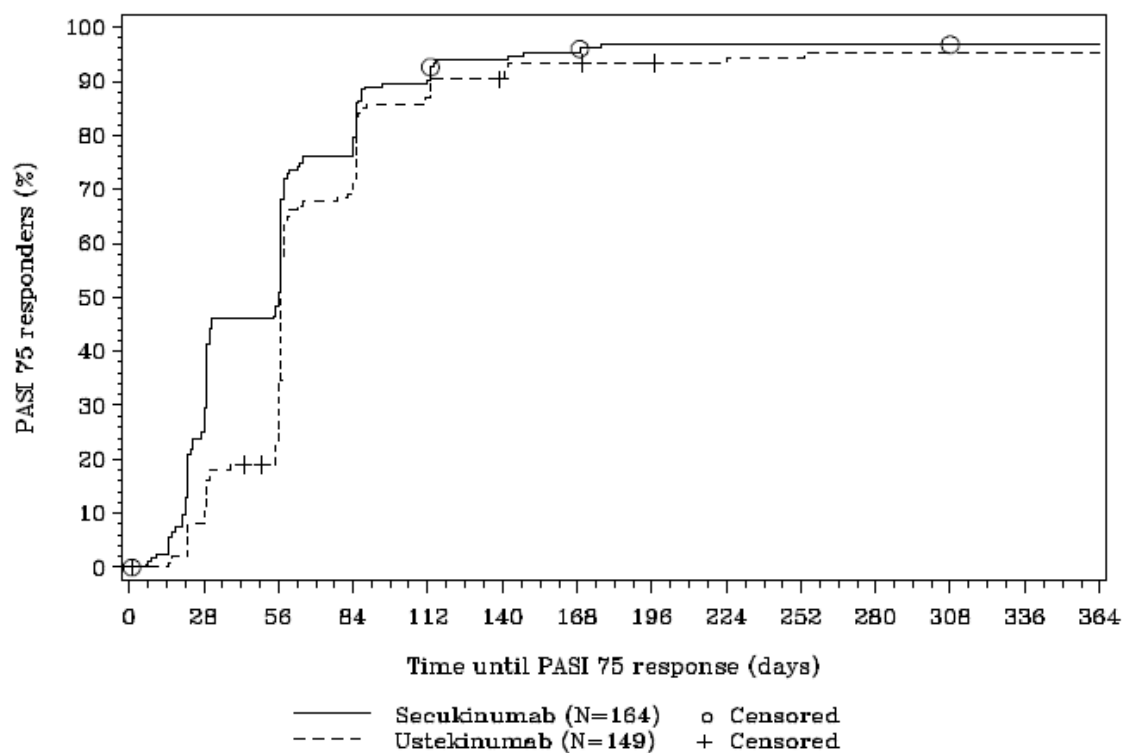
Logrank test: p-value = 0,003 **
**: p < 0,05; *: p < 0,1

Censoring occurs one day after the last regular visit. Discontinued patients are censored at day of discontinuation. Patients without any response assessment are censored at day 1

Analysis population: A2317 FAS subpopulation B (Patients with ((PASI > 10 or BSA > 10) and DL-QI > 10) and lack of efficacy or lack of tolerability or contraindication to at least 1 conventional systemic psoriasis treatment)

Figure 2: Kaplan-Meier curves for the time to first achieving PASI 90 response – RCT, direct comparison: secukinumab vs. ustekinumab

Patients at risk (Secukinumab/Ustekinumab): Day 0: 164/149, Day 28: 115/132, Day 56: 80/95, Day 84: 33/41, Day 112: 16/19, Day 140: 9/13, Day 168: 7/9, Day 196: 4/8, Day 224: 4/6, Day 252: 4/6, Day 280: 4/5, Day 308: 3/5, Day 336: 3/5, Day 364: 3/5

Logrank test: p-value = 0,008 **
**: p < 0,05; *: p < 0,1

Censoring occurs one day after the last regular visit. Discontinued patients are censored at day of discontinuation. Patients without any response assessment are censored at day 1

Analysis population: A2317 FAS subpopulation B (Patients with ((PASI > 10 or BSA > 10) and DL-QI > 10) and lack of efficacy or lack of tolerability or contraindication to at least 1 conventional systemic psoriasis treatment)

Figure 3: Kaplan-Meier curves for the time to first achieving PASI 75 response – RCT, direct comparison: secukinumab vs. ustekinumab