IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A17-08

Secukinumab (plaque psoriasis) –

Benefit assessment according to §35a Social Code Book V[1] (new scientific findings)

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Secukinumab (Plaque-Psoriasis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 May 2017). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BMI	body mass index
BSA	body surface area
DLQI	Dermatology Life Quality Index
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
MCS	Mental Component Summary
NAPSI	Nail Psoriasis Severity Index
NB-UVB	narrowband ultraviolet B
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PT	Preferred Term
PUVA	psoralen and ultraviolet-A light
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
ULN	upper limit of normal

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug secukinumab. The pharmaceutical company (hereinafter referred to as "the company") submitted a first dossier of the drug to be evaluated on 1 June 2015 for the early benefit assessment. This dossier was assessed in dossier assessment A15-20 and in the corresponding addendum A15-44. The company now requested a new benefit assessment for a subpopulation of the approved therapeutic indication because of new scientific findings. The assessment was based on a dossier compiled by the company. The dossier was sent to IQWiG on 1 March 2017.

Research question

The aim of the present report was to assess the added benefit of secukinumab in comparison with the appropriate comparator therapy (ACT) in adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy.

From the approved therapeutic indication of secukinumab, 2 subpopulations resulted from the specification of the ACT. For the present assessment, only the subpopulation of patients who are candidates for systemic therapy and/or phototherapy is relevant. The G-BA specified the ACT presented in Table 2 for this subpopulation.

Table 2: Research question of the benefit assessment of secukinumab

Therapeutic indication	**Appropriate comparator therapy**[a, b]
Adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy[c]	**Fumaric acid esters** or ciclosporin or methotrexate or phototherapy (balneotherapy, oral PUVA, NB-UVB)
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: Dosage of the ACT was to concur with the recommendations of the relevant SPCs. A dose-fair comparison under exhaustion of the approval-compliant dosage (if tolerated) was to be conducted. c: This population was only a subpopulation of the approved therapeutic indication. It included all patients in the approved therapeutic indication less the 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. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B; PUVA: psoralen and ultraviolet-A light; SPC: Summary of Product Characteristics	

The company followed the specification of the G-BA and chose fumaric acid esters from the options mentioned.

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

Results

The study CAIN457ADE06 (hereinafter referred to as "PRIME") was included in the benefit assessment.

The PRIME study was a randomized, open-label, parallel-group study comparing secukinumab with fumaric acid esters. The PRIME study included adult patients with moderate to severe plaque psoriasis who had not yet received systemic treatment. The patients had to have their disease for at least 6 months and had to be inadequately treated with previous topical treatments. The severity grade of the psoriasis in the study was defined using a Psoriasis Area and Severity Index (PASI) > 10, an affected body surface area (BSA) of > 10% and a Dermatology Life Quality Index (DLQI) of > 10.

Patients were randomly allocated in a ratio of 1:1 to treatment with secukinumab or fumaric acid esters. The total population of the study comprised 202 patients (105 patients in the secukinumab arm and 97 patients in the fumaric acid ester arm).

The administration of secukinumab concurred with the requirements of the Summary of Product Characteristics (SPC). The patients in the fumaric acid ester arm received daily oral fumaric acid esters following a defined titration scheme, which started with a low dose, followed by a dose increase until reaching a predefined treatment goal. The titration scheme complied with the requirements of the SPC.

In both study arms, treatment with secukinumab or fumaric acid esters was to be conducted for 24 weeks. Subsequent therapies in case of discontinuation of treatment or end of study participation were not restricted.

The risk of bias at study level was rated as low. The risk of bias at outcome level was rated as high for all outcomes.

Results

Due to the high risk of bias at outcome level and due to the presence of only one study, at most hints, e.g. of an added benefit, can initially be derived for all outcomes. Due to the very large effects in the outcomes "remission" (PASI 100), "discontinuation due to AEs", "gastrointestinal disorders" and "flushing", hereinafter indications are derived for these outcomes.

Mortality

- All-cause mortality

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

Morbidity

- Remission (PASI 100)

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

- NAPSI 100

There were no usable data for the outcome "Nail Psoriasis Severity Index (NAPSI) 100". This resulted in no hint of an added benefit of secukinumab in comparison with fumaric acid esters; an added benefit is therefore not proven.

Health-related quality of life

- DLQI (0 or 1)

A statistically significant result in favour of secukinumab in comparison with fumaric acid esters was shown for the outcome "DLQI (0 or 1)". Under consideration of the outcome-specific high risk of bias, this resulted in a hint of an added benefit of secukinumab in comparison with fumaric acid esters.

- SF-36

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

There was no statistically significant difference between the treatment groups for the PCS or for the MCS in the consideration of the mean differences. This resulted in no hint of an added benefit of secukinumab in comparison with fumaric acid esters; an added benefit for the outcome "SF-36" is therefore not proven.

Side effects

- Serious adverse events

No statistically significant difference between the treatment arms was shown for the outcome "serious adverse events (SAEs)". Hence there was no hint of greater or lesser harm from secukinumab; greater or lesser harm is therefore not proven.

- Discontinuation due to adverse events

A statistically significant result in favour of secukinumab in comparison with fumaric acid esters was shown for the outcome "discontinuation due to adverse events (AEs)". In addition, there was an indication of an effect modification by the characteristic "age" for this outcome.

A statistically significant difference in favour of secukinumab was shown for patients < 65 years. There was an outcome-specific high risk of bias for this outcome. Considering the size of the observed effect, however, it was not assumed that the effect and the size of the effect were caused by bias alone. Overall, this resulted in an indication of lesser harm of secukinumab in comparison with fumaric acid esters.

There was no statistically significant difference between the treatment groups for patients ≥ 65 years. The result for the total population was statistically significant. Since there was only an indication and no proof of an effect modification, the added benefit of secukinumab for patients ≥ 65 years is not principally called into question, but subject to greater uncertainty. The certainty of conclusions was therefore downgraded from "indication" to "hint". In the present data situation, the extent for patients ≥ 65 years cannot be determined using the effect estimate of the study or the effect estimate of the subgroup. For patients ≥ 65 years, this resulted in a hint of lesser harm of non-quantifiable extent.

- Specific adverse events

No statistically significant difference between the treatment arms was shown for the outcome "infections and infestations". Hence there was no hint of greater or lesser harm from secukinumab; greater or lesser harm is therefore not proven.

A statistically significant advantage of secukinumab in comparison with fumaric acid esters was shown for the outcome "blood and lymphatic system disorders". Under consideration of the risk of bias, this resulted in a hint of lesser harm of secukinumab in comparison with fumaric acid esters.

A statistically significant advantage of secukinumab in comparison with fumaric acid esters was shown for the outcomes "gastrointestinal disorders" and "flushing". There was an outcome-specific high risk of bias for these outcomes. Considering the size of the observed effects, however, it was not assumed that the effects, or the size of the effects, were caused by bias alone. Overall, this resulted in an indication of lesser harm of secukinumab in comparison with fumaric acid esters in each case.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the probability and extent of the added benefit of the drug secukinumab compared with the ACT is assessed as follows:

In the overall consideration, there were only positive effects for secukinumab in comparison with fumaric acid esters.

The positive effects included an indication of considerable added benefit in the category "morbidity" for the outcome "remission" (PASI 100). In addition, there was a hint of a major added benefit in the category "health-related quality of life" for the outcome "DLQI (0 or 1)". There were further positive effects in the category "non-serious/non-severe side effects". For the outcome "discontinuation due to AEs", there was an indication of lesser harm of considerable extent for patients < 65 years and a hint of lesser harm of non-quantifiable extent for patients ≥ 65 years. There was an indication of lesser harm of considerable extent for each of the outcomes "gastrointestinal disorders" and "flushing". For the outcome "blood and lymphatic system disorders", there was a hint of lesser harm of considerable extent.

In summary, there is an indication of considerable added benefit of secukinumab in comparison with the ACT fumaric acid esters for patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy.

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

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].

Table 3: Secukinumab – probability and extent of added benefit

Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
Adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy[c]	**Fumaric acid esters** or ciclosporin or methotrexate or phototherapy (balneotherapy, oral PUVA, NB-UVB)	Indication of considerable added benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: Dosage of the ACT was to concur with the recommendations of the relevant SPCs. A dose-fair comparison under exhaustion of the approval-compliant dosage (if tolerated) was to be conducted.
c: This population was only a subpopulation of the approved therapeutic indication. It included all patients in the approved therapeutic indication less the 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.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B; PUVA: psoralen and ultraviolet-A light; SPC: Summary of Product Characteristics

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

2.2 Research question

The aim of the present report was to assess the added benefit of secukinumab in comparison with the ACT in adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy.

From the approved therapeutic indication of secukinumab, 2 subpopulations resulted from the specification of the ACT (see Section 1.1 of the full dossier assessment and assessments A15-20 and A15-44 [1,2]). For the present assessment, only the subpopulation of patients who are candidates for systemic therapy and/or phototherapy is relevant. The G-BA specified the ACT presented in Table 4 for this subpopulation.

Table 4: Research question of the benefit assessment of secukinumab

Therapeutic indication	Appropriate comparator therapy[a, b]
Adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy[c]	**Fumaric acid esters** or ciclosporin or methotrexate or phototherapy (balneotherapy, oral PUVA, NB-UVB)

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: Dosage of the ACT was to concur with the recommendations of the relevant SPCs. A dose-fair comparison under exhaustion of the approval-compliant dosage (if tolerated) was to be conducted.
c: This population was only a subpopulation of the approved therapeutic indication. It included all patients in the approved therapeutic indication less the 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.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B; PUVA: psoralen and ultraviolet-A light; SPC: Summary of Product Characteristics

The company specified fumaric acid esters as ACT for adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy. This concurred with the specification of the G-BA, which had specified further treatment options as ACT for this research question besides fumaric acid esters with ciclosporin or methotrexate or phototherapy (balneotherapy, oral psoralen and ultraviolet-A light [PUVA], narrowband ultraviolet B [NB-UVB]).

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on secukinumab (status: 8 December 2016)
- bibliographical literature search on secukinumab (last search on 7 December 2016)
- search in trial registries for studies on secukinumab (last search on 7 December 2016)

To check the completeness of the study pool:

- search in trial registries for studies on secukinumab (last search on 1 March 2017)

No additional relevant study was identified from the check.

2.3.1 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: secukinumab vs. fumaric acid esters

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
CAIN457ADE06 (PRIME[b])	No	Yes	No
a: Study for which the company was sponsor. b: In the following tables, the study is referred to with this abbreviated form. RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of secukinumab corresponded to that of the company. In the PRIME study, secukinumab was directly compared with fumaric acid esters.

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: secukinumab vs. fumaric acid esters

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PRIME	RCT, open-label, parallel	▪ Adults (≥ 18 years) with moderate to severe plaque psoriasis (PASI score > 10, BSA > 10% and DLQI > 10) at the start of the study ▪ diagnosis of the disease at least 6 months before randomization ▪ topical treatment alone no longer adequate ▪ without prior systemic treatment	Secukinumab (N = 105) fumaric acid esters (N = 97)	Screening: 1–4 weeks Treatment: 24 weeks	33 study centres in Germany 4/2015–6/2016	Primary: PASI 75 response at week 24 Secondary: remission (PASI 100 response), symptoms, health-related quality of life, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes.

AE: adverse event; BSA: body surface area; DLQI: Dermatology Life Quality Index; N: number of randomized patients; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: secukinumab vs. fumaric acid esters

Study	Intervention	Comparison
PRIME	Secukinumab 300 mg, 2 x 150 mg SC in weeks 0, 1, 2, 3, 4, 8, 12, 16 and 20 no dose adjustments allowed	Daily dose following titration scheme[a] **Fumaric acid esters INITIAL[b]:** week 0: 1 tablet in the evening week 1: 1 tablet in the morning and 1 in the evening week 2: 1 tablet in the morning, 1 at midday and 1 in the evening (until the last tablet of a 40-tablet blister pack has been taken) **Fumaric acid esters[c]:** week 2–3: 1 tablet in the evening week 4: 1 tablet in the morning and 1 in the evening week 5: 1 tablet in the morning, 1 at midday and 1 in the evening week 6: 1 tablet in the morning, 1 at midday and 2 in the evening week 7: 2 tablets in the morning, 1 at midday and 2 in the evening week 8–24: 2 tablets in the morning, 2 at midday and 2 in the evening
	Pretreatment: Permitted pretreatment: ▪ topical psoriasis treatment until at most 2 weeks before randomization ▪ systemic corticosteroids (oral, IV, intramuscular, SC, intraarticular, transdermal) for less than 8 weeks, discontinued at least 4 weeks before randomization ▪ phototherapy (e.g. UVA, UVB, balneo-phototherapy without psoralen or other UV-enhancing bath additives) until at most 2 weeks before randomization Non-permitted pretreatment: ▪ IL-17A- or IL-17RA-targeted biologics ▪ immunomodulators (e.g. alefacept, efalizumab, adalimumab, infliximab, ustekinumab, etanercept, golimumab, certolizumab, methotrexate, ciclosporin, cyclophosphamide) ▪ systemic corticosteroids (oral, IV, intramuscular, SC, intraarticular, transdermal) for more than 8 weeks ▪ fumaric acid esters ▪ systemic psoriasis treatment (e.g. retinoids) ▪ photochemotherapy (e.g. PUVA or balneo-phototherapy with psoralen or other UV-enhancing bath additives) **Concomitant treatment:** Allowed concomitant treatment: ▪ drugs that can worsen psoriasis (e.g. beta-blockers, lithium) at least 4 weeks before randomization at a stable dose ▪ emollients for scaling and/or itching without pharmacologically active ingredients Non-permitted concomitant treatment: ▪ live vaccines ▪ topical treatment with mild- to high-potency corticosteroids[d] ▪ cytostatic drugs, drugs with nephrotoxic potential	

(continued)

Table 7: Characteristics of the intervention – RCT, direct comparison: secukinumab vs. fumaric acid esters (continued)

a: Dose increase was possible due to the investigator's decision for the following reasons: not reaching the treatment goal of a mean improvement of the PASI score of ≥ 75% in comparison with the start of the study, after dose reduction and not reaching the treatment goal or after reaching the treatment goal if the advantage of the dose increase is considered greater than the risk of AEs.
b: Composed of: 30 mg dimethyl fumarate, 67 mg calcium salt of ethyl fumarate, 5 mg magnesium salt of ethyl hydrogen fumarate, 3 mg zinc salt of ethyl hydrogen fumarate.
c: Composed of: 120 mg dimethyl fumarate, 87 mg calcium salt of ethyl fumarate, 5 mg magnesium salt of ethyl hydrogen fumarate, 3 mg zinc salt of ethyl hydrogen fumarate.
d: Based on strength and body region discontinued 2 weeks to 1 day before randomization.
AE: adverse event; DLQI: Dermatology Life Quality Index; IL-17A: interleukin-17A; IL-17RA: interleukin-17 receptor A; IV: intravenous; PASI: Psoriasis Area and Severity Index; PUVA: psoralen and ultraviolet-A light; RCT: randomized controlled trial; SC: subcutaneous; UVA: ultraviolet-A light; UVB: ultraviolet-B light; vs.: versus

The PRIME study was a randomized, open-label, parallel-group study comparing secukinumab with fumaric acid esters. The study was conducted in 33 study centres in Germany. The study included adult patients with moderate to severe plaque psoriasis who had not yet received systemic treatment. The patients had to have their disease for at least 6 months and had to be inadequately treated with previous topical treatments. The severity grade of the psoriasis in the study was defined using a PASI > 10, an affected BSA of > 10% and a DLQI of > 10.

The population investigated in the study concurred with the population relevant for the research question. The patients included were randomly allocated in a ratio of 1:1 to treatment with secukinumab or fumaric acid esters. The total population of the study comprised 202 patients (105 patients in the secukinumab arm and 97 patients in the fumaric acid ester arm).

The patients in the secukinumab arm received 300 mg secukinumab at week 0, 1, 2, 3, 4, 8, 12, 16 and 20. Dose adjustments were not allowed. This concurs with the requirements of the SPC [5].

The patients in the fumaric acid ester arm received daily oral fumaric acid esters following a defined titration scheme (see Table 7), which started with a low dose, followed by a dose increase until reaching the treatment goal. The titration scheme complied with the requirements of the SPC [6]. The treatment goal was defined as a 75% improvement of the PASI (PASI 75 response). On reaching the treatment goal, the dose was to be reduced to the minimum required dose for maintaining the treatment goal. It was at the investigator's discretion, however, to maintain or further increase the dose if the advantage for the patient was greater than the risk of AEs. If the treatment goal could not be reached, it was at the investigator's discretion to determine a 50% improvement of the PASI with presence of a DLQI of ≤ 5 as treatment goal. Since the treatment goal was defined as a 75% improvement of the PASI, it is possible that the fumaric acid ester dose was not uptitrated to the

individually best possible treatment success in all patients, resulting in a disadvantage in reaching remission in this treatment arm. This led to an uncertainty in the interpretation of the outcomes that went beyond a PASI 75 response, e.g. PASI 100 and DLQI (0 or 1) (see Section 2.4.2 and Section 2.7.2.4.2 of the full dossier assessment).

According to the SPC [6], the fumaric acid ester dose had to be immediately halved in patients whose lymphocyte count decreased to < 700/µL. Treatment was to be discontinued immediately in patients with an increase in serum creatinine above normal (> 1 upper limit of normal [ULN]), unless the investigator considered this increase to be clinically irrelevant. According to the SPC, in contrast, treatment discontinuation is required in any creatinine increase above normal. There is no uniform definition of the reference values, however, so that the deviation has no consequence for the present benefit assessment.

Previous medication that was considered necessary for the patients' health and was not part of the psoriasis treatment could be continued. In addition, emollients without pharmacologically active ingredients were allowed as concomitant treatment. Systemic treatments for plaque psoriasis were not allowed as pretreatment or as concomitant treatment. Photo- or photochemotherapy (e.g. PUVA or balneo-phototherapy) and topical treatments with pharmacologically active ingredients were not allowed as concomitant treatment.

In both study arms, treatment with secukinumab or fumaric acid esters was to be conducted for 24 weeks. Subsequent therapies in case of discontinuation of treatment or end of study participation were not restricted.

Primary outcome of the study was the PASI 75 response, i.e. an improvement in psoriasis score by at least 75% at week 24 versus baseline. Relevant secondary outcomes were remission (PASI 100 response), symptoms, health-related quality of life and side effects.

The outcomes included, except the outcomes on side effects, were recorded up to 24 weeks. Side effects were recorded up to 30 days after the last study medication or the last study visit.

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

Table 8: Characteristics of the study population – RCT, direct comparison: secukinumab vs. fumaric acid esters

Study **Characteristics** **Category**	**Secukinumab**	**Fumaric acid esters**
PRIME	N[a] = 105	N[a] = 97
Age [years], mean (SD)	43 (14)	42 (13)
Sex [F/M], %	38/62	38/62
BMI [kg/m^2], mean (SD)	29.3 (6.7)	29.6 (7.6)
Ethnicity, n (%)		
Caucasian	102 (97.1)	97 (100.0)
Black	1 (1.0)	0 (0)
Asian	2 (1.9)	0 (0)
Other	0 (0)	0 (0)
Smoking status, n (%)		
Never	32 (30.5)	30 (30.9)
Current	55 (52.4)	56 (57.7)
Former	18 (17.1)	11 (11.3)
Time since first diagnosis [years], mean (SD)	16.2 (12.7)	16.4 (13.2)
Known psoriatic arthritis, n (%)	4 (3.8)	8 (8.2)
Prior topical medication, n (%)	105 (100.0)	97 (100.0)
Fingernails affected, n (%)	56 (53.3)	49 (51.6)
Toenails affected, n (%)	50 (47.6)	42 (44.2)
Treatment discontinuation[b], n (%)	6 (5.7)	54 (55.7)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Treatment discontinuation was considered as study discontinuation in the study. Patients who discontinued treatment were asked to come to a last visit at week 24. According to the study documents, data on all relevant outcomes were to be recorded at this visit. 5 of the patients who discontinued treatment came to the visit at week 24. The main reason for treatment discontinuation in the fumaric acid ester arm was AEs (32 of 54 patients, 59%).
AE: adverse event; BMI: body mass index; F: female; M: male; n: number of patients in the category; N: number of randomized (or included) patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patient characteristics were sufficiently comparable between the 2 study arms. The patients in the PRIME study had a mean age of just over 40 years. The majority of the patients were male and Caucasian. The mean body mass index (BMI) was just under 30 kg/m^2 in both study arms. Half of the patients were current smokers. The mean time since first diagnosis of plaque psoriasis was about 16 years, and few patients also had known psoriatic arthritis. In half the patients in each case, the plaque psoriasis affected fingernails or toenails. All patients had been treated with topical medication before inclusion into the study.

During the study, more than half of the patients in the fumaric acid ester arm discontinued treatment and therefore the study. AEs were the main reason for treatment discontinuation. In comparison, only a total of about 6% of the patients in the secukinumab discontinued treatment and the study.

Table 9 shows the mean/median treatment duration of the patients.

Table 9: Information on the course of the study – RCT, direct comparison: secukinumab vs. fumaric acid esters

Study **Duration of the study phase** **Outcome category**	**Secukinumab**	**Fumaric acid esters**
PRIME	N[a] = 105	N[a] = 95
Treatment duration [days]		
Median [min; max]	168 [44; 193]	120 [1; 180]
Mean (SD)	165 (23)	113 (59)

a: Data refer to the patient numbers of the safety analysis.
max: maximum; min: minimum; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Due to the large differences in treatment and study discontinuation rates between the treatment arms, the median treatment duration was notably longer in the secukinumab arm (168 days) than in the fumaric acid ester arm (120 days). This resulted in different observation periods for the outcomes.

Table 10 shows the risk of bias at study level.

Table 10: Risk of bias at study level – RCT, direct comparison: secukinumab vs. fumaric acid esters

Study	**Adequate random sequence generation**	**Allocation concealment**	**Blinding**		**Reporting independent of the results**	**No additional aspects**	**Risk of bias at study level**
			Patient	**Treating staff**			
CAIN457ADE06 (PRIME)	Yes	Yes	No	No[a]	Yes	No[b]	Low

a: Blinded recording of outcomes for PASI and NAPSI.
b: In a large proportion of patients in the fumaric acid ester arm (70.1%), the protocol was violated in the study because the drug was not administered in compliance with the protocol. The study documents did not contain further information on this.
NAPSI: Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; vs.: versus

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

Limitations resulting from the open-label study design and the protocol violations in the fumaric acid ester arm are described in Section 2.4 with the outcome-specific risk of bias.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - remission (PASI 100)
  - NAPSI 100
- Health-related quality of life
  - DLQI (0 or 1)
  - SF-36
- Side effects
  - SAEs
  - discontinuation due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.2.4.3 of the full dossier assessment).

The outcomes "PASI 75" and "PASI 90" presented by the company were not considered to be patient-relevant and were therefore not used for the derivation of an added benefit. The results on the PASI 75 and the PASI 90 are presented as additional information, however.

The company presented different types of analysis for the outcomes it presented. Due to the high rates of patients who discontinued treatment and the resulting different observation periods between the treatment arms, time-adjusted analyses and analyses using multiple imputation of imputed values were used in the present benefit assessment. The observed 2x2 tables were used for the outcomes "all-cause mortality" and "discontinuation due to AEs" (see Section 2.7.2.4.3 of the full dossier assessment for reasons).

Table 11 shows for which outcomes data were available in the studies included.

Table 11: Matrix of outcomes – RCT, direct comparison: secukinumab vs. fumaric acid esters

Study	Outcomes										
	All-cause mortality	**Remission (PASI 100)[a]**	**NAPSI 100[a]**	**Health-related quality of life (DLQI 0 or 1)**	**Health-related quality of life (SF-36)**	**SAEs**	**Discontinuation due to AEs**	**Infections and infestations (SOC)**	**Blood and lymphatic system disorders (SOC)**	**Gastrointestinal disorders (SOC)**	**Flushing (PT)**
PRIME	Yes	Yes	No[b]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: Improvement in score by 100% compared with start of the study.
b: No usable data available; for reasons, see Section 2.7.2.4.3 of the full dossier assessment.
AE: adverse event; DLQI: Dermatology Life Quality Index; NAPSI: Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index, PT: Preferred Term; RCT: randomized controlled trial; SF-36: Short Form (36) Health Survey; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

2.4.2 Risk of bias

Table 12 shows the risk of bias for the relevant outcomes.

Table 12: Risk of bias at study and outcome level – RCT, direct comparison: secukinumab vs. fumaric acid esters

Study		Outcomes										
	Study level	**All-cause mortality**	**Remission (PASI 100)[a]**	**NAPSI 100[a]**	**Health-related quality of life (DLQI 0 or 1)**	**Health-related quality of life (SF-36)**	**SAEs**	**Discontinuation due to AEs**	**Infections and infestations (SOC)**	**Blood and lymphatic system disorders (SOC)**	**Gastrointestinal disorders (SOC)**	**Flushing (PT)**
PRIME	L	H[b]	H[c]	-[d]	H[c, e]	H[e, f]	H[c]	H[b, e]	H[c, e]	H[c, e]	H[c, e]	H[c, e]

a: Improvement in PASI or NAPSI score by 100% compared with start of the study.
b: Large proportion of patients or large difference between the treatment groups regarding the proportion of patients imputed using LOCF (all-cause mortality: 5.7% secukinumab vs. 49.5% fumaric acid esters; discontinuation due to AEs: 3.8% secukinumab vs. 14.7% fumaric acid esters).
c: Potentially large difference in potentially informative censorings between the treatment groups.
d: No usable data.
e: Lack of blinding in subjective recording of outcomes.
f: Large proportion or large difference between the treatment groups regarding the proportion of patients imputed using multiple imputation (17.1% secukinumab vs. 56.8% fumaric acid esters).
AE: adverse event; DLQI: Dermatology Life Quality Index; H: high; L: low; NAPSI: Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index, PT: Preferred Term; RCT: randomized controlled trial; SF-36: Short Form (36) Health Survey; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

The risk of bias of all outcomes included was rated as high. This deviates from the assessment of the company, which rated the risk of bias for the outcomes "all-cause mortality", "remission" (PASI 100) and "NAPSI 100" as low and for all other outcomes as high.

There were no usable data for the outcome "NAPSI 100" (see Section 2.7.2.4.3 of the full dossier assessment for reasons). The risk of bias was therefore not assessed. This deviates from the assessment of the company, which used the NAPSI 100 data.

The high risk of bias for the outcomes "all-cause mortality" and "discontinuation due to AEs" resulted from the large proportion of patients imputed using the last observation carried forward (LOCF) method.

The high risk of bias for the outcomes "remission" (PASI 100), "DLQI (0 or 1)" and the outcomes of the category of side effects (except discontinuation due to AEs) resulted from the potentially large differences in potentially informative censorings between the treatment groups.

The risk of bias for the outcome "health-related quality of life" (SF-36) was rated as high because there was a large proportion or a large difference between the treatment groups regarding the proportion of patients imputed using multiple imputation.

The high risk of bias for the outcomes of the category of health-related quality of life (DLQI [0 or 1], SF-36) and for the outcomes of the category of side effects (except SAEs) resulted from the lack of blinding in subjective outcomes.

Since the treatment goal was defined as a PASI 75 response and therefore a disadvantage in achieving remission could not be excluded because the dose was not further uptitrated in the fumaric acid ester arm, the risk of bias of the outcomes that went beyond a PASI 75 response was increased. In addition, the risk of bias of all outcomes was increased by the high number of protocol violations because fumaric acid esters were not used in compliance with the protocol.

2.4.3 Results

Table 13, Table 14 and Table 15 summarize the results on the comparison of secukinumab with fumaric acid esters in patients with plaque psoriasis.

Where necessary, the data from the company's dossier were supplemented with the Institute's calculations. If available, Kaplan-Meier curves on the outcomes included are presented in Appendix A of the full dossier assessment.

Table 13: Results (mortality) – RCT, direct comparison: secukinumab vs. fumaric acid esters

Study Outcome	Secukinumab		Fumaric acid esters		Secukinumab vs. fumaric acid esters
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
PRIME					
Mortality					
All-cause mortality	105	0 (0)	95	0 (0)	NC

CI: confidence interval; n: number of patients with (at least 1) event; NC: not calculated; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 14: Results (morbidity, health-related quality of life [dichotomous], side effects) – RCT, direct comparison: secukinumab vs. fumaric acid esters

Study Outcome category Outcome	Secukinumab N	Secukinumab Median time to event in months [95% CI] Patients with event n (%)	Fumaric acid esters N	Fumaric acid esters Median time to event in months [95% CI] Patients with event n (%)	Secukinumab vs. fumaric acid esters HR [95% CI]; p-value[a]
PRIME					
Morbidity					
PASI					
Remission (PASI 100)	105	5.55 [3.71; NA] 47.59 (45.32)[b]	95	NA 6.08 (6.40)[b]	25.65 [6.17; 106.66] < 0.001
Response (PASI 90)	*105*	*1.97 [1.87; 2.46]* *80.29 (76.47)[b]*	*95*	*5.82 [5.59; NA]* *29.04 (30.57)[b]*	*9.75 [5.08; 18.72]* *< 0.001*
Response (PASI 75)	*105*	*1.35 [0.99; 1.41]* *96.64 (92.04)[b]*	*95*	*4.63 [4.07; 5.68]* *45.38 (47.77)[b]*	*9.84 [5.51; 17.57]* *< 0.001*
NAPSI	No usable data[c]				
Health-related quality of life					
DLQI (0 or 1)	105	2.33 [1.87; 2.79] 75.26 (71.68)[d]	95	5.68 [5.55; NA] 33.34 (35.09)[d]	4.49 [2.69; 7.47] < 0.001
Side effects					
AEs (supplementary information)	105	0.76 [0.43; 1.25] 88 (83.81)	95	0.33 [0.20; 0.46] 90 (94.74)	-
SAEs	105	NA 4 (3.81)	95	NA 4 (4.21)	1.22 [0.26; 5.62] 0.802
Infections and infestations	105	2.83 [1.68; 5.09] 66 (62.86)	95	2.86 [2.53; 4.37] 51 (53.68)	1.11 [0.74; 1.67] 0.610
Blood and lymphatic system disorders	105	NA 6 (5.71)	95	NA 35 (36.84)	0.11 [0.05; 0.26] < 0.001
Gastrointestinal disorders	105	NA 23 (21.90)	95	0.79 (0.62; 1.28) 81 (85.26)	0.09 [0.05; 0.17] < 0.001
Flushing	105	NA 1 (0.95)	95	NA 34 (35.79)	0.02 [0.00; 0.16]; < 0.001
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
Discontinuation due to AEs	105	2 (1.90)	95	38 (40.00)	0.05 [0.01; 0.19] < 0.001[f]

(continued)

Table 14: Results (morbidity, health-related quality of life [dichotomous], side effects) – RCT, direct comparison: secukinumab vs. fumaric acid esters (continued)

a: Effect, CI and p-value: Cox proportional hazards model.
b: Data of the analysis at week 24 with imputation of missing values using multiple imputation. The effect estimate for the relevant outcome "remission" (PASI 100) is RR = 7.45; 95% CI [2.60; 21.35]; p < 0.001.
c: The analysis only included patients with affected nails at the start of the study. Patients whose nails became affected during the study were not recorded. In addition, the proportion of analysed patients was below 70% at all time points (see Section 2.7.2.4.3 of the full dossier assessment).
d: Data of the analysis at week 24 with imputation of missing values using multiple imputation. The effect estimate is RR = 2.06; 95% CI [1.36; 3.12]; p = 0.001.
e: Institute's calculation, unconditional exact test (CSZ method according to [7]).
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; HR: hazard ratio; n: number of patients with (at least 1) event; NA: not achieved; NAPSI: Nail Psoriasis Severity Index; NC: not calculated; ND: no data; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 15: Results (health-related quality of life, continuous) – RCT, direct comparison: secukinumab vs. fumaric acid esters

Study **Outcome category** **Outcome**	**Secukinumab**			**Fumaric acid esters**			**Secukinumab vs. fumaric acid esters**
	N[a]	**Values at start of study an (SD)**	**Change at week 24 mean[b] (SE)**	**N[a]**	**Values at start of study n (SD)**	**Change at week 24 mean[b] (SE)**	**MD [95% CI]; p-value[b]**
PRIME							
Health-related quality of life							
SF-36							
PCS	105	48.23 (8.22)	6.13 (0.74)	95	48.03 (9.12)	5.13 (1.02)	1.01 [−1.13; 3.14] 0.355
MCS	105	39.98 (11.98)	11.56 (0.95)	95	40.69 (11.31)	9.31 (1.25)	2.24 [−0.35; 4.84] 0.090

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-values: ANCOVA of the changes between start and end of the study, adjusted for study centre and baseline values, with imputation of missing values using multiple imputation.
ANCOVA: analysis of covariance; CI: confidence interval; MCS: Mental Component Summary score; MD: mean difference; N: number of analysed patients; PCS: Physical Component Summary score; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SF-36: Short Form (36) Health Survey; vs.: versus

The company did not address the probability of the added benefit or the harm at outcome level. It derived an indication of an added benefit in the overall consideration of the results. It additionally provided its extent for some outcomes. Hereinafter, it is therefore not described to what extent the assessment of the individual outcomes deviates from that of the company.

The risk of bias for all outcomes was assessed as high. Because of this and due to the presence of only one study, at most hints, e.g. of an added benefit, can initially be derived for all outcomes. Due to the very large effects in the outcomes "remission" (PASI 100), "discontinuation due to AEs", "gastrointestinal disorders" and "flushing", hereinafter indications are derived for these outcomes.

Mortality

All-cause mortality

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

Morbidity

Remission (PASI 100)

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

NAPSI 100

There were no usable data for the outcome "NAPSI 100". This resulted in no hint of an added benefit of secukinumab in comparison with fumaric acid esters; an added benefit is therefore not proven.

Health-related quality of life

DLQI (0 or 1)

A statistically significant result in favour of secukinumab in comparison with fumaric acid esters was shown for the outcome "DLQI (0 or 1)". Under consideration of the outcome-specific high risk of bias, this resulted in a hint of an added benefit of secukinumab in comparison with fumaric acid esters.

SF-36

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

There was no statistically significant difference between the treatment groups for the PCS or for the MCS in the consideration of the mean differences. This resulted in no hint of an added benefit of secukinumab in comparison with fumaric acid esters; an added benefit for the outcome "SF-36" is therefore not proven.

Side effects

Serious adverse events

No statistically significant difference between the treatment arms was shown for the outcome "SAEs". Hence there was no hint of greater or lesser harm from secukinumab; greater or lesser harm is therefore not proven.

Discontinuation due to adverse events

A statistically significant result in favour of secukinumab in comparison with fumaric acid esters was shown for the outcome "discontinuation due to AEs".

In addition, there was an indication of an effect modification by the characteristic "age" for this outcome (see Section 2.4.4). The high risk of bias and the size of the observed effects were also considered in this case. For patients < 65 years, this resulted in an indication of lesser harm of secukinumab in comparison with fumaric acid esters. For patients ≥ 65 years, under consideration of the result from the total population, this resulted in a hint of lesser harm of secukinumab in comparison with fumaric acid esters.

Specific adverse events

Infections and infestations (System Organ Class [SOC])

No statistically significant difference between the treatment arms was shown for the outcome "infections and infestations". Hence there was no hint of greater or lesser harm from secukinumab; greater or lesser harm is therefore not proven.

Blood and lymphatic system disorders (SOC)

A statistically significant advantage of secukinumab in comparison with fumaric acid esters was shown for the outcome "blood and lymphatic system disorders". Under consideration of the risk of bias, this resulted in a hint of lesser harm of secukinumab in comparison with fumaric acid esters.

Gastrointestinal disorders (SOC)

A statistically significant advantage of secukinumab in comparison with fumaric acid esters was shown for the outcome "gastrointestinal disorders". There was an outcome-specific high risk of bias for this outcome. Considering the size of the observed effect, however, it was not assumed that the effect and the size of the effect were caused by bias alone. Overall, this resulted in an indication of lesser harm of secukinumab in comparison with fumaric acid esters.

Flushing (Preferred Term [PT])

A statistically significant advantage of secukinumab in comparison with fumaric acid esters was shown for the outcome "flushing". There was an outcome-specific high risk of bias for this outcome. Considering the size of the observed effect, however, it was not assumed that

the effect and the size of the effect were caused by bias alone. Overall, this resulted in an indication of lesser harm of secukinumab in comparison with fumaric acid esters.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered to be relevant in the present benefit assessment:

- age (< 65 years, ≥ 65 years)
- sex (men, women)
- disease severity (moderate: PASI ≤ 20, BSA ≤ 20%/severe: PASI > 20, BSA > 20)

The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification. Due to the different proportions of imputed values in the treatment groups and of the potentially informative censoring because of discontinuation due to AEs and withdrawal of informed consent, only results with proof of an interaction were considered for all outcomes, except for the outcome "discontinuation due to AEs" (see Section 2.7.2.2 of the full dossier assessment). In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least 1 subgroup.

The subgroup results of secukinumab in comparison with fumaric acid esters are summarized in Table 16. Where necessary, the data from the dossier were supplemented by the Institute's calculations.

Table 16: Subgroups (discontinuation due to AEs) – RCT, direct comparison: secukinumab vs. fumaric acid esters

Study **Outcome**	**Secukinumab**		**Fumaric acid esters**		**Secukinumab vs. fumaric acid esters**	
Characteristic **Subgroup**	**N**	**Patients with event** **n (%)**	**N**	**Patients with event** **n (%)**	**RR [95% CI]**	**p-value**
PRIME						
Discontinuation due to AEs						
Age						
< 65 years	98	1 (1.02)	88	34 (38.64)	0.03 [0.00; 0.19]	< 0.001
≥ 65 years	7	1 (14.29)	7	4 (57.14)	0.25 [0.04; 1.71]	0.158
					Interaction:	0.076[a]

a: Institute's calculation, p-value from Q test for heterogeneity.
CI: confidence interval; G-BA: Federal Joint Committee; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; vs.: versus

The results of the PRIME study showed an indication (p = 0.076) of an effect modification by the characteristic "age" for the outcome "discontinuation due to AEs".

A statistically significant difference in favour of secukinumab was shown for patients < 65 years. There was an outcome-specific high risk of bias for this outcome. Considering the size of the observed effect, however, it was not assumed that the effect and the size of the effect were caused by bias alone. Overall, this resulted in an indication of lesser harm of secukinumab in comparison with fumaric acid esters.

There was no statistically significant difference between the treatment groups for patients ≥ 65 years. The result for the total population was statistically significant. Since there was only an indication and no proof of an effect modification, the added benefit of secukinumab for patients ≥ 65 years is not principally called into question, but subject to greater uncertainty. The certainty of conclusions was therefore downgraded from "indication" to "hint". In the present data situation, the extent for patients ≥ 65 years cannot be determined using the effect estimate of the study or the effect estimate of the subgroup. For patients ≥ 65 years, this resulted in a hint of lesser harm of non-quantifiable extent.

This deviates from the assessment of the company, which identified no indication or proof of an effect modification by the characteristic "age".

2.5 Probability and extent of added benefit

The derivation of probability and extent 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 [1].

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

2.5.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 resulted in the following assessment of secukinumab in comparison with fumaric acid esters:

- an indication of an added benefit for the outcome "remission" (PASI 100)
- a hint of an added benefit for the outcome "DLQI (0 or 1)"
- an indication of lesser harm for the outcome "discontinuation due to AEs" for patients < 65 years
- a hint of lesser harm for the outcome "discontinuation due to AEs" for patients ≥ 65 years
- a hint of lesser harm for the outcome "blood and lymphatic system disorders"

- an indication of lesser harm for each of the outcomes “gastrointestinal disorders” and “flushing”

The extent of the respective added benefit at outcome level was estimated from these results (see Table 17).

Table 17: Extent of added benefit at outcome level: secukinumab vs. fumaric acid esters

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Secukinumab vs. fumaric acid esters** **Median time to event or proportion of events or mean change** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	Proportion: 0% vs. 0%	Added benefit not proven
Morbidity		
Remission (PASI 100)	Median: 5.55 months vs. NA HR: 25.65 [6.17; 106.66] HR[c]: 0.04 [0.01; 0.16] p < 0.001 probability: “indication”[d]	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: “considerable”
NAPSI 100	No usable data	Lesser benefit/added benefit not proven
Health-related quality of life		
DLQI (0 or 1)	Median: 2.33 vs. 5.68 months HR: 4.49 [2.69; 7.47] HR[c]: 0.22 [0.13; 0.37] p < 0.001 probability: “hint”	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5%[e] added benefit, extent: “major”
SF-36		
PCS	Mean: 6.13 vs. 5.13 MD: 1.01 [−1.13; 3.14] p = 0.355	Lesser benefit/added benefit not proven
MCS	Mean: 11.56 vs. 9.31 MD: 2.24 [−0.35; 4.84] p = 0.090	Lesser benefit/added benefit not proven
Side effects		
Serious adverse events	Median: NA vs. NA HR: 1.22 [0.26; 5.62] p = 0.802	Greater/lesser harm not proven

(continued)

Table 17: Extent of added benefit at outcome level: secukinumab vs. fumaric acid esters (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Secukinumab vs. fumaric acid esters** **Median time to event or proportion of events or mean change** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Discontinuation due to AEs	Proportion: 1.90% vs. 40.00% RR: 0.05 [0.01; 0.19] p < 0.001	
Age		
< 65 years	Proportion: 1.02% vs. 38.64% RR: 0.03 [0.00; 0.19] p < 0.001 probability: "indication"[d]	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
≥ 65 years	Proportion: 14.29% vs. 57.14% RR: 0.25 [0.04; 1.71] p = 0.158 probability: "hint"	Outcome category: non-serious/non-severe side effects lesser harm, extent: "non-quantifiable"
Infections and infestations	Median: 2.83 vs. 2.86 months HR: 1.11 [0.74; 1.67] p = 0.610	Greater/lesser harm not proven
Blood and lymphatic system disorders	Median: NA vs. NA HR: 0.11 [0.05; 0.26] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
Gastrointestinal disorders	Median: NA vs. 0.79 months HR: 0.09 [0.05; 0.17] p < 0.001 probability: "indication"[d]	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
Flushing	Median: NA vs. NA HR: 0.02 [0.00; 0.16] p < 0.001 probability: "indication"[d]	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"

(continued)

Table 17: Extent of added benefit at outcome level: secukinumab vs. fumaric acid esters (continued)

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CIu.
c: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d: The certainty of results is considered high because it cannot be assumed that the observation of such a large effect is explicable solely by the aspects of bias (lack of blinding, highly different proportions between the treatment groups of imputed patients in the analysis or great differenced in potentially informative censorings).
e: No information on the proportion of patients at risk for the event time analysis, but the as-observed analysis showed that more than 5% of the patients were at risk at week 24.
AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; DLQI: Dermatology Life Quality Index; HR: hazard ratio; MCS: Mental Component Summary score; MD: mean difference; NA: not achieved; PASI: Psoriasis Area and Severity Index; PCS: Physical Component Summary score; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of secukinumab in comparison with fumaric acid esters

Positive effects	**Negative effects**
Morbidity ▪ Non-serious/non-severe symptoms/late complications ▫ Remission (PASI 100): indication of an added benefit – extent: "considerable"	–
Health-related quality of life ▪ DLQI (0 or 1): hint of an added benefit – extent: "major"	
Non-serious/non-severe side effects ▪ Discontinuation due to AEs ▫ Age - < 65 years: indication of lesser harm – extent: "considerable" - ≥ 65 years: hint of lesser harm – extent: "non-quantifiable" ▪ Blood and lymphatic system disorders: hint of lesser harm – extent: "considerable" ▪ Gastrointestinal disorders: indication of lesser harm – extent: "considerable" ▪ Flushing: indication of lesser harm – extent: "considerable"	
AE: adverse event; DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index	

In the overall consideration, there were only positive effects for secukinumab in comparison with fumaric acid esters.

For the total population, the positive effects included an indication of considerable added benefit in the category "morbidity" for the outcome "remission" (PASI 100). In addition, there was a hint of a major added benefit in the category "health-related quality of life" for the outcome "DLQI (0 or 1)". There were further positive effects in the category "non-serious/non-severe side effects". For the outcome "discontinuation due to AEs", there was an indication of lesser harm of considerable extent for patients < 65 years and a hint of lesser harm of non-quantifiable extent for patients ≥ 65 years. There was an indication of lesser harm of considerable extent for each of the outcomes "gastrointestinal disorders" and "flushing". For the outcome "blood and lymphatic system disorders", there was a hint of lesser harm of considerable extent.

In summary, there is an indication of considerable added benefit of secukinumab in comparison with the ACT fumaric acid esters for patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy.

The result of the assessment of the added benefit of secukinumab in comparison with the ACT is summarized in Table 19.

Table 19: Secukinumab – probability and extent of added benefit

Therapeutic indication	**Appropriate comparator therapy[a, b]**	**Probability and extent of added benefit**
Adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy[c]	**Fumaric acid esters** or ciclosporin or methotrexate or phototherapy (balneotherapy, oral PUVA, NB-UVB)	Indication of considerable added benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: Dosage of the ACT was to concur with the recommendations of the relevant SPCs. A dose-fair comparison under exhaustion of the approval-compliant dosage (if tolerated) was to be conducted.
c: This population was only a subpopulation of the approved therapeutic indication. It included all patients in the approved therapeutic indication less the 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.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B; PUVA: psoralen and ultraviolet-A light; SPC: Summary of Product Characteristics

This deviates from the approach of the company, which derived an indication of major added benefit for the population of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy.

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

2.6 List of included studies

Novartis Pharma. A 24-week, randomized, controlled, multicenter, open-label study with blinded assessment of the efficacy of subcutaneous secukinumab compared to Fumaderm in adults with moderate to severe plaque psoriasis [online]. In: EU Clinical Trials Register. [Accessed: 15.03.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-005258-20.

Novartis. A 24-week, randomized, controlled, multicenter, open-label study with blinded assessment of the efficacy of subcutaneous secukinumab compared to Fumaderm in adults with moderate to severe plaque psoriasis: study CAIN457ADE06; clinical study report [unpublished]. 2017.

Novartis. A 24-week, randomized, controlled, multicenter, open-label study with blinded assessment of the efficacy of subcutaneous secukinumab compared to Fumaderm in adults with moderate to severe plaque psoriasis: study CAIN457ADE06; clinical trial protocol [unpublished]. 2015.

Novartis. A 24-week, randomized, controlled, multicenter, open-label study with blinded assessment of the efficacy of subcutaneous secukinumab compared to Fumaderm in adults with moderate to severe plaque psoriasis: study CAIN457ADE06; Zusatzanalysen [unpublished]. 2017.

Novartis Pharmaceuticals. Study of secukinumab compared to Fumaderm in adults with moderate to severe psoriasis: (PRIME); full text view [online]. In: ClinicalTrials.gov. 23.09.2016 [Accessed: 15.03.2017]. URL: https://clinicaltrials.gov/show/NCT02474082.

References for English extract

Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a17-08-secukinumab-plaque-psoriasis-benefit-assessment-according-to-35a-social-code-book-v-new-scientific-findings.7845.html.