IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Secukinumab – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 August 2015). 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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Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Michael Weichenthal, University Medical Center Schleswig-Holstein, Kiel, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment[2]:

- Ana Liberman
- Petra Kohlepp
- Mandy Kromp
- Ulrike Lampert
- Ulrike Seay
- Volker Vervölgyi
- Carolin Weigel

Keywords: secukinumab, psoriasis, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSA	body surface area
DLQI	Dermatology Life Quality Index
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IGA mod 2011	Investigator's global assessment modified 2011
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
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale

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 assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 1 June 2015.

Research question

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

Depending on the pretreatment, 2 research questions result from this. These are shown in Table 2.

Table 2: Research questions and ACT for secukinumab

Research question	Therapeutic indication	ACT[a]
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 or phototherapy (balneo-phototherapy, oral PUVA, NB-UVB)
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**

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. The company chose methotrexate as only comparator therapy for research question A.
b: This population includes all patients in the approved therapeutic indication without the patients named in research question B.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B; PUVA: psoralen and ultraviolet-A light

The G-BA specified individually optimized standard treatment under consideration of fumaric acid esters or cyclosporine or methotrexate or phototherapy as ACT for research question A. Deviating from the G-BA, the company chose methotrexate as only comparator therapy. For research question B, the company followed the G-BA's specification and chose ustekinumab as only ACT. The present assessment was conducted in comparison with the G-BA's ACT.

The assessment was conducted based on patient-relevant outcomes and on the evidence provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were to be included in the assessment.

Results for research question A: patients with plaque psoriasis who are candidates for systemic therapy

The company presented no studies of direct comparisons for research question A.

The company presented an indirect comparison of secukinumab with methotrexate using the common comparator placebo. The indirect comparison was unsuitable for the benefit assessment because the studies included by the company did not fulfil the minimum study duration of 24 weeks. Since plaque psoriasis is a chronic disease, which requires long-term treatment, a minimum study duration of 24 weeks was considered necessary for the assessment of the added benefit.

However, the study duration for the randomized comparison was only 12 weeks in each of the studies presented by the company for the secukinumab side of the indirect comparison (CAIN457A2223, ERASURE, FIXTURE, FEATURE and JUNCTURE). On the methotrexate side, the study duration for the randomized comparison of the presented study CHAMPION was 16 weeks. Moreover it is unclear whether the ACT of individually optimized treatment was implemented in the indirect comparison, particularly in the CHAMPION study due to its comparison (methotrexate versus placebo).

There were therefore no relevant data for the assessment of the added benefit of secukinumab in adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy. Hence there was no hint of an added benefit of secukinumab in comparison with the ACT. An added benefit is therefore not proven.

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

One relevant study (CAIN457A2317) was available for the benefit assessment.

Study characteristics

The CAIN457A2317 study was a multicentre, randomized, double-blind parallel group study. Secukinumab was compared with ustekinumab in the study. Patients with moderate to severe plaque psoriasis who had had the disease for at least 6 months and for whom previous treatments with topical therapy or phototherapy or systemic treatment had been inadequate were included in the study. Hence the CAIN457A2317 study also included patients who had not yet received systemic treatment. However, the company presented analyses of a subpopulation of the CAIN457A2317 study, in which only those patients were included in whom at least one previous systemic treatment had failed. The patients included in these analyses are an adequate representation of the subpopulation relevant for research question B and were therefore used for the benefit assessment.

In the secukinumab arm, patients received 300 mg secukinumab once weekly as induction treatment in the first 4 weeks, and then once every 4 weeks as maintenance treatment. Patients in the ustekinumab arm received weight-related injections with 45 mg or 90 mg ustekinumab at the start of the study, at week 4 and then every 12 weeks. In the second treatment phase, the treatment regimen of maintenance treatment was continued.

The study is still ongoing, and the present assessment was based on analyses of a planned interim analysis after 24 weeks.

Risk of bias

The risk of bias at study and outcome level for the CAIN457A2317 study was rated as low.

Mortality

All-cause mortality

No deaths occurred in the CAIN457A2317 study up to treatment week 24. There was no hint of an added benefit of secukinumab in comparison with ustekinumab; an added benefit is therefore not proven.

Morbidity

Remission (Psoriasis Area and Severity Index [PASI] 100)

There was no statistically significant difference between the intervention and the control group for the outcome "remission" recorded with the PASI 100. Hence there was no hint of an added benefit of secukinumab in comparison with ustekinumab; an added benefit is therefore not proven.

Symptoms: pain, itching, scaling

There was no statistically significant difference between the intervention and the control group for symptoms recorded with the outcomes **"pain"**, **"itching"** and **"scaling"**. Hence there was no hint of an added benefit of secukinumab in comparison with ustekinumab; an added benefit is therefore not proven.

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

There were no evaluable data 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

Dermatology Life Quality Index (DLQI)

There were no evaluable data for the outcome "DLQI". Hence there was no hint of an added benefit of secukinumab in comparison with ustekinumab; an added benefit is therefore not proven.

Adverse events

There was no statistically significant difference between the intervention and the control group for the outcomes **"serious adverse events (SAEs)"** and **"discontinuation due to adverse events (AEs)"**. Hence there was no hint of greater or lesser harm from secukinumab; greater or lesser harm is therefore not proven.

There was no statistically significant difference between the intervention and the control group for the outcome **"infections and infestations"**. However, there was proof of an effect modification by the characteristic "sex" for this outcome. It was therefore meaningful to consider the results separately for men and women. The difference between the treatment arms remained not statistically significant in men. In women, there was a statistically significant result in favour of secukinumab; the extent was no more than marginal, however. Hence there was no hint of greater or lesser harm from secukinumab for men or for women; greater or lesser harm is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

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

In summary, there is no added benefit of secukinumab in comparison with the ACT for adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy (research question A). There is also no added benefit of secukinumab in comparison with the ACT for adult 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 (research question B).

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

Research question	Therapeutic indication	ACT[a]	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**	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: This population includes all patients in the approved therapeutic indication without 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.

2.2 Research question

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

Two research questions (A and B) resulted from this, for which the G-BA specified the ACTs presented in Table 4.

Table 4: Research questions of the benefit assessment of secukinumab

Research question	Therapeutic indication	ACT[a]
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)
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**

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 without the patients named in research question B.
c: The company chose methotrexate as only comparator therapy. This approach was not followed (see Section 2.6.1 of the full dossier assessment).
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B; PUVA: psoralen and ultraviolet-A light

For easier presentation and better readability, the report uses the following terms for the 2 therapeutic indications:

- patients with plaque psoriasis who are candidates for systemic therapy (research question A)
- patients with plaque psoriasis with inadequate response to other systemic treatments or who are unsuitable for these treatments (research question B)

The G-BA specified individually optimized standard treatment under consideration of fumaric acid esters or cyclosporine or methotrexate or phototherapy as ACT for research question A. Deviating from the G-BA, the company chose methotrexate as only comparator therapy (see Section 2.6.1 of the full dossier assessment). For research question B, the company followed the G-BA's specification and chose ustekinumab as only ACT. The present assessment was conducted in comparison with the G-BA's ACT.

The assessment was conducted based on patient-relevant outcomes and on the evidence provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were to be included in the assessment.

2.3 Research question A (patients with plaque psoriasis who are candidates for systemic therapy)

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on secukinumab (status: 17 April 2015)
- bibliographical literature search on secukinumab (last search on 10 March 2015)
- search in trial registries for studies on secukinumab (last search on 23 March 2015)
- bibliographical literature search on the ACT (last search on 10 March 2015)
- search in trial registries for studies on the ACT (last search on 10 March 2015)

To check the completeness of the study pool:

- search in trial registries for studies on secukinumab (last search on 15 June 2015)

No RCT on the direct comparison of secukinumab with the ACT was identified from the check of the completeness of the study pool. This concurs with the company's assessment. Since the company identified no RCTs of direct comparison, the company conducted an indirect comparison according to Bucher [3] of secukinumab versus methotrexate with placebo as common comparator. The study pool of the company was unsuitable for the indirect comparison of secukinumab with the ACT. This is justified below.

Study pool of the company for the indirect comparison

The study pool of the company included 5 RCTs on the comparison of secukinumab with placebo: CAIN457A2223 [4], ERASURE [5], FIXTURE [5], FEATURE [6], JUNCTURE [7]. The company identified one RCT (the study CHAMPION [8]) for the comparison of methotrexate with placebo.

The characteristics and interventions of the studies for the indirect comparison are presented in Table 24 and Table 25 in Appendix B of the full dossier assessment.

The indirect comparison presented by the company could not be used for the benefit assessment for the following reasons:

Plaque psoriasis is an incurable chronic disease requiring long-term treatment. In clinical studies, at first response to treatment is to be assessed after an induction phase of 8 to

12 weeks [9]. It is then necessary to continue observing the patients to explore the duration of response to treatment. Hence a study duration of at least 24 weeks is considered necessary for assessing the added benefit of plaque psoriasis treatments. This assessment concurs with the recommendations of the regulatory authority. Both the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E1 guideline [10] and the European Medicines Agency (EMA) guideline on the conduct of studies with psoriasis patients [9] demand a study duration of at least 24 weeks. It should also be noted that the company specified a minimum study duration of 24 weeks for the direct comparison of secukinumab with the ACT (for research questions A and B). In each of the studies on the secukinumab side of the indirect comparison, the study duration for the randomized comparison was 12 weeks; in the CHAMPION study on the methotrexate side, the study duration for the randomized comparison was 16 weeks. Hence none of the studies met the inclusion criterion of a minimum study duration of 24 weeks.

Moreover it is unclear whether the ACT of individually optimized treatment was implemented in the indirect comparison, particularly in the CHAMPION study due to its comparison (methotrexate versus placebo) (see Section 2.6.1 of the full dossier assessment).

In summary, the studies presented by the company for the indirect comparison for the assessment of the added benefit of secukinumab in comparison with the ACT were unsuitable.

2.3.2 Results on added benefit

There were no relevant data for the assessment of the added benefit of secukinumab in adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy. Hence there was no hint of an added benefit of secukinumab in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit

Since the company presented no relevant data for adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and/or phototherapy, an added benefit of secukinumab is not proven.

2.3.4 List of included studies

Not applicable as the company presented no relevant studies on the comparison of secukinumab in comparison with the ACT specified by the G-BA.

2.4 Research question B (patients with plaque psoriasis with inadequate response to other systemic treatments or who are unsuitable for these treatments)

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on secukinumab (status: 17 April 2015)
- bibliographical literature search on secukinumab (last search on 10 March 2015)
- search in trial registries for studies on secukinumab (last search on 23 March 2015)

To check the completeness of the study pool:

- search in trial registries for studies on secukinumab (last search on 15 June 2015)

No additional relevant study was identified from the check.

2.4.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: secukinumab vs. ustekinumab

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
CAIN457A2317	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of secukinumab corresponded to that of the company. Secukinumab was directly compared with ustekinumab in the included study CAIN457A2317.

Section 2.4.4 contains a reference list for the study included.

2.4.1.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison: secukinumab vs. ustekinumab

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CAIN 457A2317	RCT, double-blind, parallel	Adults with moderate to severe chronic plaque psoriasis (PASI ≥ 12 and BSA ≥ 10% and IGA mod 2011 ≥ 3, with inadequate control under topical treatment and/or phototherapy and/or previous systemic treatment)[b]	Secukinumab (N = 337) ustekinumab (N = 339) Relevant subpopulation thereof[b]: secukinumab (n = 164) ustekinumab (n = 149)	▪ Screening: 1-4 weeks ▪ Treatment phase 1: up to week 16 ▪ Treatment phase 2: up to week 52 ▪ Treatment phase 3: up to week 104[c]	Worldwide in 134 study centres: Australia, Austria, Belgium, Bulgaria, Canada, Denmark, Estonia, France, Germany, Greece, Hungary, Israel, Italy, Korea, Netherlands, Norway, Portugal, Slovakia, Spain, Switzerland, Taiwan, Turkey, United Kingdom, United States of America 2/2014–ongoing[d]	Primary: remission PASI 90 at week 16 Secondary: remission (PASI 100), 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 for this benefit assessment.
b: The company used the following criteria to define the relevant subpopulation: (PASI > 10 or BSA > 10%) and DLQI > 10 as well as failure of or intolerance or contraindication to at least one other conventional systemic psoriasis treatment. According to the inclusion criteria of the study, only patients with PASI ≥ 12 were included in the study (see Section 2.6.2.4.1 of the full dossier assessment).
c: Treatment phase 3 was conducted under secukinumab up to week 104, and under ustekinumab until database closure after 52 weeks. Then treatment with ustekinumab ended, and patients under secukinumab could continue the study as open-label treatment.
d: Interim analysis at week 24.

AE: adverse event; BSA: body surface area; DLQI: Dermatology Life Quality Index; IGA mod 2011: Novartis Investigator's Global Assessment modified 2011; N: number of randomized patients; n: relevant subpopulation; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: secukinumab vs. ustekinumab

Study	Intervention	Comparison
CAIN457A2317	Secukinumab 300 mg (twice 150 mg), subcutaneous injection ▪ week 0, 1, 2 and 3: once weekly ▪ starting from week 4: once every 4 weeks (up to week 104)	Ustekinumab 45 mg, subcutaneous injection (90 mg for a baseline body weight of > 100 kg) + placebo for secukinumab[a], subcutaneous injection ▪ week 0 and 4: once each ▪ then once each every 12 weeks (until database closure at week 52)
	Prohibited concomitant treatment: ▪ drug-containing topical treatments, e.g. with salicylic acid, urea, corticosteroids ▪ phototherapy ▪ other systemic psoriasis treatments Allowed concomitant treatment: ▪ drug-free topical treatments	

a: Secukinumab and ustekinumab were administered with different dosing schemes. Secukinumab placebo was used in a way that the treatment arms could not be distinguished by the dosing frequency. Ustekinumab placebo was not necessary for blinding.
RCT: randomized controlled trial; vs.: versus

The CAIN457A2317 study is a randomized, double-blind, parallel-group study conducted in 134 study centres worldwide. Secukinumab was compared with ustekinumab in the study. Patients with moderate to severe plaque psoriasis with a PASI ≥ 12, an Investigator's global assessment modified 2011 (IGA mod 2011) ≥ 3 and an affected body surface area (BSA) of ≥ 10% were included in the study. The patients had to have their disease for at least 6 months and had to be inadequately treated with previous topical treatments or phototherapy or systemic treatment. Hence besides patients treated with inadequate systemic treatment, the CAIN457A2317 study also included patients who had not yet received systemic treatment. Moreover, also patients who had already received systemic treatment that had not failed before the start of the study were included. However, the company presented analyses of a subpopulation of the CAIN457A2317 study, in which only those patients were included in whom at least one previous systemic treatment had failed. The patients included in these analyses are an adequate representation of the subpopulation relevant for research question B and were therefore used for the benefit assessment (see Section 2.6.2.3.2 of the full dossier assessment).

The patients included were randomly assigned in a ratio of 1:1 to secukinumab (N = 337) or to ustekinumab (N = 339). The relevant subpopulation comprised n = 164 patients in the secukinumab arm, and n = 149 patients in the ustekinumab arm of the study.

The first treatment phase was 16 weeks. In the secukinumab arm, patients received 300 mg secukinumab once weekly in the form of 2 injections as induction treatment in the first 4 weeks, and then once every 4 weeks as maintenance treatment. Patients in the ustekinumab arm received weight-related injections with 45 mg or 90 mg ustekinumab at the start of the study, at week 4 and then every 12 weeks. In addition, patients in the ustekinumab arm received placebo injections for secukinumab. In the second treatment phase up to week 52, the treatment regimen of maintenance treatment was continued. The study is still ongoing, and the present assessment was based on analyses of a planned interim analysis after 24 weeks.

After database closure in the second treatment phase, patients are unblinded. For patients in the ustekinumab arm, the study ends at that time point. Patients in the secukinumab arm continue treatment with 300 mg secukinumab every 4 weeks, either up to week 104 or until secukinumab is commercially available.

Patients were not allowed to receive drug-containing topical treatments, phototherapy or other systemic psoriasis treatments besides the study medication.

The company presented analyses at week 24 for most outcomes (see Section 2.6.2.4.3 of the full dossier assessment). For the outcome category “health-related quality of life” and for the outcome “health status”, the company only presented analyses at week 16. These were not evaluable for the benefit assessment because an observation period of 16 weeks is not considered sufficient according to the specification of the minimum study duration (see Section 2.3.1).

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

Table 8: Characteristics of the study populations – RCT, direct comparison: secukinumab vs. ustekinumab

Study Group	N[a]	Age [years] mean (SD)	Sex [F/M] %[b]	Disease severity [moderate/ severe][c] %	Time since first diagnosis [years] mean (SD)	Number of patients pretreated with ≥ 1 systemic treatment n (%)	Treatment discontin-uations n (%)	Study discontin-uations n (%)
CAIN457A2317								
Secukinumab	164	44 (14)	35/65	26.8/73.2	18.8 (12.4)	164 (100)	8 (2.4)[d]	ND
Ustekinumab	149	44 (14)	32/69	30.9/69.1	17.0 (10.8)	149 (100)	17 (5.0)[d]	ND

a: Number of patients in the relevant subpopulation.
b: Deviation from 100% possible because of rounding.
c: Moderate: between (PASI ≥ 10 or BSA ≥ 10%) and (PASI ≤ 20 and BSA ≤ 20%) as well as DLQI > 10; severe: BSA > 20% or PASI > 20 as well as DLQI > 10.
d: Data for the total study population. There is no information for the relevant subpopulation.

BSA: body surface area; DLQI: Dermatology Life Quality Index; F: female; M: male; N: number of randomized (or included) patients; n: number of patients; ND: no data; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

There were no important differences between the treatment groups with regard to age and sex. The mean age of the patients was 44 years. Notably more men than women were included in both study arms with the distribution being comparable. Regarding disease severity, the vast majority of the patients had severe plaque psoriasis. Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: secukinumab vs. ustekinumab

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			
CAIN457A2317	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for the CAIN457A2317 study was rated as low. This concurs with the company's assessment.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - remission (PASI 100)
  - symptoms: pain, itching, scaling
  - health status (EQ-5D VAS)
- Health-related quality of life
  - DLQI
- Adverse events
  - SAES
  - discontinuation due to AEs
  - infections and infestations (System Organ Class [SOC])

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in its dossier (Module 4 A) (see Section 2.6.2.4.3 of the full dossier assessment).

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

Table 10: Matrix of outcomes – RCT, direct comparison: secukinumab vs. ustekinumab

Study	Outcomes									
	All-cause mortality	Remission (PASI 100)[a]	Symptoms (pain)[b]	Symptoms (itching)[b]	Symptoms (scaling)[b]	Health status (EQ-5D VAS)	Health-related quality of life (DLQI)	SAEs	Discontinuation due to AEs	Infections and infestations
CAIN457A2317	Yes	Yes	Yes	Yes	Yes	No[c]	No[c]	Yes	Yes	Yes

a: Improvement on PASI score by 100% compared with baseline.
b: Recorded on a numerical scale (0-10).
c: No evaluable data available for the relevant subpopulation at week 24; see Section 2.6.2.4.3 of the full dossier assessment for reasons.
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

2.4.2.2 Risk of bias

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

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: secukinumab vs. ustekinumab

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

a: Improvement on PASI score by 100% compared with baseline.
b: Recorded on a numerical scale (0-10).
c: No evaluable data available for the relevant subpopulation at week 24; see Section 2.6.2.4.3 of the full dossier assessment for reasons.
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 for all outcomes included in the assessment was rated as low. This concurs with the company's assessment.

2.4.2.3 Results

Table 12 and Table 13 summarize 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. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. Only the results at the analysis date of 24 weeks were used in the present benefit assessment.

Table 12: Results (dichotomous outcomes) – RCT, direct comparison: secukinumab vs. ustekinumab

Study **Outcome category** **Outcome**	**Secukinumab**		**Ustekinumab**		**Secukinumab vs. ustekinumab**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
CAIN457A2317					
Mortality					
All-cause mortality	163	0	148	0	NC
Morbidity					
Remission (PASI 100)	163	73 (44.8)	148	50 (33.8)	1.33 [1.00; 1.76]; 0.051
Adverse events					
AEs	163	126 (77.3)	148	114 (77.0)	
SAEs	163	7 (4.3)	148	5 (3.4)	1.27 [0.41; 3.92]; 0.732
Discontinuation due to AEs	163	4 (2.5)	148	1 (0.7)	3.63 [0.41; 32.13]; 0.256
Infections and infestations	163	69 (42.3)	148	64 (43.2)	0.98 [0.76; 1.27]; 0.897

a: Institute's calculation, unconditional exact test (CSZ method according to [11]).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with (at least one) event; NC: not calculable; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 13: Results (continuous outcomes) – RCT, direct comparison: secukinumab vs. ustekinumab

Study Outcome category Outcome	Secukinumab			Ustekinumab			Secukinumab vs. ustekinumab
	N[a]	Baseline values mean (SE)	Change at week 24[b] mean[c] (SE)	N[a]	Baseline values mean (SE)	Change at week 24[b] mean[c] (SE)	MD [95% CI]; p-value
CAIN457A2317							
Morbidity							
Symptoms							
Pain	162	5.17 (0.24)	-4.13 (0.15)	147	5.06 (0.24)	-4.19 (0.16)	0.07 [-0.32; 0.46]; 0.734
Itching	162	7.43 (0.17)	-5.76 (0.17)	147	7.29 (0.17)	-5.72 (0.18)	-0.04 [-0.48; 0.39]; 0.841
Scaling	162	7.64 (0.18)	-6.37 (0.16)	147	7.54 (0.17)	-6.19 (0.17)	-0.17 [-0.60; 0.25]; 0.430
Health status (EQ-5D VAS)	No evaluable data						
Health-related quality of life							
DLQI	No evaluable data						

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: Negative changes indicate improvement of symptoms on a 0-10 scale.
c: Unless stated otherwise, LOCF analysis of the FAS population.
CI: confidence interval; DLQI: Dermatology Life Quality Index; 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

No deaths occurred in the CAIN457A2317 study up to treatment week 24. There was no hint of an added benefit of secukinumab in comparison with ustekinumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Remission (PASI 100)

There was no statistically significant difference between the intervention and the control group for the outcome "remission" recorded with the PASI 100. Hence there was no hint of an added benefit of secukinumab in comparison with ustekinumab; an added benefit is therefore not proven.

For remission recorded with the PASI 100, this concurs with the company's assessment. However, based on different operationalizations of the PASI (mean PASI score; PASI 75 and PASI 90), the company derived an added benefit of secukinumab.

Symptoms: pain, itching, scaling

There was no statistically significant difference between the intervention and the control group for each of the symptoms recorded with the outcomes **"pain"**, **"itching"** and **"scaling"**. Hence there was no hint of an added benefit of secukinumab in comparison with ustekinumab; an added benefit is therefore not proven.

This assessment concurs with that of the company, which also derived no added benefit for these outcomes.

Health status (EQ-5D VAS)

There were no evaluable data 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.

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

Health-related quality of life

Dermatology Life Quality Index

There were no evaluable data for the outcome "DLQI". Hence there was no hint of an added benefit of secukinumab in comparison with ustekinumab; an added benefit is therefore not proven.

This assessment deviates from that of the company, which derived an added benefit for this outcome.

Adverse events

The AEs that most commonly occurred in the CAIN457A2317 study are presented in Appendix A of the full dossier assessment. There were no lists of common SAEs and discontinuations due to AEs for the relevant subpopulation.

There was no statistically significant difference between the intervention and the control group for the outcomes **"SAEs"** and **"discontinuation due to AEs"**. Hence there was no hint of greater or lesser harm from secukinumab; greater or lesser harm is therefore not proven.

There was no statistically significant difference between the intervention and the control group for the outcome **"infections and infestations"**. However, there was proof of an effect modification by the characteristic "sex" for this outcome. It was therefore meaningful to consider the results separately for men and women.

The subgroup analyses showed no hint of greater or lesser harm from secukinumab for men or for women; greater or lesser harm is therefore not proven.

This assessment concurs with that of the company, which also derived no added benefit for these outcomes.

2.4.2.4 Subgroups and other effect modifiers

Selected subgroups were investigated for the presence of heterogeneous treatment effects in order to detect possible effect differences.

The following subgroup characteristics were included in the assessment:

- age
- sex
- disease severity
- pretreatment with biologics
- region

Hereinafter only the results on subgroups and outcomes with at least indications of an interaction between treatment effect and subgroup characteristic and with statistically significant results in at least one subgroup are presented. The prerequisite for proof of differing effects is a statistically significant homogeneity and/or interaction test ($p < 0.05$). An indication of differing effects results from a p-value between 0.05 and 0.2.

Table 14 shows the results of the subgroup analyses.

Table 14: Subgroups (dichotomous outcomes): infections and infestations by sex – RCT, direct comparison: secukinumab vs. ustekinumab

Study Outcome	Secukinumab		Ustekinumab		Secukinumab vs. ustekinumab	
Characteristic Subgroup	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
CAIN457A2317						
Infections and infestations						
Sex						
Men	105	48 (45.7)	102	38 (37.3)	1.23 [0.88; 1.70]	0.220
Women	58	21 (36.2)	46	26 (56.5)	0.64 [0.42; 0.98]	0.040
					Interaction:	0.018[a]

a: Institute's calculation from meta-analysis (Cochran's Q test).
CI: confidence interval; N: number of analysed patients; n: number of patients with (at least one) event; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Adverse events

Infections and infestations

There was proof of an effect modification by the characteristic "sex" for the outcome "infections and infestations".

There was no statistically significant difference between the intervention and the control group for men. Hence for men there was no hint of greater or lesser harm from secukinumab; greater or lesser harm is therefore not proven.

There was a statistically significant difference in favour of secukinumab for women. The extent in this outcome of the outcome category "non-serious/non-severe AEs" was no more than marginal, however. Hence there was no hint of greater or lesser harm from secukinumab; greater or lesser harm is therefore not proven.

This concurs with the company's assessment, which did not use the subgroup results for deriving the added benefit.

2.4.3 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 [1].

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

2.4.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.4.2 resulted in no hint of an added benefit or greater or lesser harm from secukinumab in comparison with ustekinumab for patients with plaque psoriasis with inadequate response to other systemic treatments or who are unsuitable for these treatments.

Table 15 shows the derivation of the added benefit at outcome level.

Table 15: Extent of added benefit at outcome level: secukinumab vs. ustekinumab

Outcome category **Outcome**	**Secukinumab vs. ustekinumab** **proportion of events/mean change** **effect estimate [95% CI]** **p-value**	**Derivation of extent**[a]
Mortality		
Deaths	0% vs. 0%	added benefit not proven
Morbidity		
Remission (PASI 100)	44.8% vs. 33.8% RR: 1.33 [1.00; 1.76] p = 0.051	Added benefit not proven
Symptoms		
Pain	-4.13 vs. -4.19 MD: 0.07 [-0.32; 0.46] p = 0.734	Added benefit not proven
Itching	-5.76 vs. -5.72 MD: -0.04 [-0.48; 0.39] p = 0.841	Added benefit not proven
Scaling	-6.37 vs. -6.19 MD: -0.17 [-0.60; 0.25] p = 0.430	Added benefit not proven
Health status (EQ-5D VAS)	No evaluable data	
Health-related quality of life		
DLQI	No evaluable data	
Adverse events		
SAEs	4.3% vs. 3.4% RR: 1.27 [0.41; 3.92] p = 0.732	Greater/lesser harm not proven
Discontinuation due to AEs	2.5% vs. 0.7% RR: 3.63 [0.41; 32.13] p = 0.256	Greater/lesser harm not proven
Infections and infestations		
Men	45.7% vs. 37.3% RR: 1.23 [0.88; 1.70] p = 0.220	Greater/lesser harm not proven
Women	36.2% vs. 56.5% RR: 0.64 [0.42; 0.98] p = 0.040	Outcome category: non-serious/non-severe AEs $0.90 \leq CI_u < 1$ greater/lesser harm not proven[b]

a: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
b: Lesser or greater harm is not proven because the effect size was only marginal.
AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; DLQI: Dermatology Life Quality Index; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; MD: mean difference; PASI: Psoriasis Area and Severity Index; RR: relative risk; SAE: serious adverse event; vs.: versus

2.4.3.2 Overall conclusion on added benefit

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

Table 16: Positive and negative effects from the assessment of secukinumab in comparison with ustekinumab

Positive effects	Negative effects
-	-

There are neither positive nor negative effects for patients with plaque psoriasis with inadequate response to other systemic treatments or who are unsuitable for these treatments

In summary, an added benefit of secukinumab in comparison with the ACT is not proven for 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.

2.4.4 List of included studies

CAIN457A2317

Novartis. A 52-week, multicenter, randomized, double-blind study of subcutaneous secukinumab to demonstrate efficacy as assessed by Psoriasis Area and Severity Index at 16 weeks of treatment compared to ustekinumab and to assess long-term safety, tolerability and efficacy in subjects with moderate to severe plaque psoriasis: study CAIN457A2317; clinical trial protocol [unpublished]. 2014.

Novartis. A 52-week, multicenter, randomized, double-blind study of subcutaneous secukinumab to demonstrate efficacy as assessed by Psoriasis Area and Severity Index at 16 weeks of treatment compared to ustekinumab and to assess long-term safety, tolerability and efficacy in subjects with moderate to severe plaque psoriasis (CLEAR): study CAIN457A2317; primary endpoint clinical study report [unpublished]. 2015.

Novartis. Secukinumab/Cosentyx: study AIN457A2317 (CLEAR); AMNOG analysis; full combined document; primary analysis [unpublished]. 2015.

Novartis. Secukinumab/Cosentyx: study AIN457A2317 (CLEAR); AMNOG analysis; subgroup analysis of relevant adverse effects; primary analysis [unpublished]. 2015.

Novartis Pharma Services. A 52-week, multicenter, randomized, double-blind study of subcutaneous secukinumab to demonstrate efficacy as assessed by Psoriasis Area and Severity Index at 16 weeks of treatment compared to ustekinumab [online]. In: EU Clinical Trials Register. [Accessed: 5 August 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-003434-32.

Novartis Pharmaceuticals. Efficacy of secukinumab compared to ustekinumab in patients with plaque-type psoriasis: full text view [online]. In: ClinicalTrials.gov. 23 December 2014 [accessed: 9 March 2015]. URL: http://ClinicalTrials.gov/show/NCT02074982.

2.5 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 17.

Table 17: Secukinumab – extent and probability of added benefit

Research question	Therapeutic indication	ACT[a]	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**	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: This population includes all patients in the approved therapeutic indication without the patients named in research question B.
c: The company chose methotrexate as only comparator therapy. This approach was not followed (see Section 2.6.1 of the full dossier assessment).
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B; PUVA: psoralen and ultraviolet-A light

In summary, there is no added benefit of secukinumab in comparison with the ACT for patients with plaque psoriasis who are candidates for systemic therapy (research question A) or for patients with plaque psoriasis with inadequate response to other systemic treatments or who are unsuitable for these treatments (research question B). This overall assessment deviates from that of the company, which claimed a hint of considerable added benefit for patients with plaque psoriasis who are candidates for systemic therapy. The company claimed an indication of considerable added benefit for patients with plaque psoriasis with inadequate response to other systemic treatments or who are unsuitable for these treatments.

References for English extract

Please see full dossier assessment for full reference list.

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