IQWiG Reports – Commission No. A20-78

Secukinumab (plaque psoriasis in children and adolescents) –

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 (Plaque-Psoriasis bei Kindern und Jugendlichen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 November 2020). 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
BSA	body surface area
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IGA mod	Investigator Global Assessment modified 2011
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IRT	interactive response technology
PASI	Psoriasis Area and Severity Index
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

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 is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 31 August 2020.

Due to the working conditions during the Corona pandemic, the present assessment was made without using strictly confidential data in Module 5 of the company's dossier.

Research question

The aim of the present report is the assessment of the added benefit of secukinumab in comparison with etanercept as appropriate comparator therapy (ACT) in children and adolescents from the age of 6 years with moderate to severe plaque psoriasis who are candidates for systemic therapy.

Table 2: Research question of the benefit assessment of secukinumab

Therapeutic indication	**ACT**[a]
Children and adolescents from the age of 6 years with moderate to severe plaque psoriasis who are candidates for systemic therapy	Adalimumab or **etanercept** or ustekinumab[b]
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. The respective approval of the drugs is to be considered. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

From the 3 alternatives, the company chose etanercept as ACT.

Etanercept is approved for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Thus, the approved therapeutic indication of etanercept covers only a part of the approved therapeutic indication of secukinumab.

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

Results

The company used the study CAIN457A2310 for the derivation of the added benefit. This RCT is unsuitable for the assessment of the added benefit of secukinumab in comparison with the ACT specified by the G-BA. In the following, the study is described and it is explained for which reasons no added benefit can be derived from the available data.

Study design

The CAIN457A2310 study is an RCT comparing 2 different dosages of secukinumab (low dose, high dose) with etanercept and placebo. The study included 162 children and adolescents aged 6 to < 18 years with severe plaque psoriasis. The investigator had to consider systemic therapy to be indicated, either because the patients had not responded adequately to topical therapies, systemic therapies or phototherapy, or because they had not tolerated systemic therapies or phototherapy. In terms of the severity of plaque psoriasis, the children and adolescents included in the CAIN457A2310 study represent only part of the population for which secukinumab is approved (moderate to severe plaque psoriasis). The comparator therapy etanercept, on the other hand, is only approved for children and adolescents with severe plaque psoriasis who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies, but not as the first systemic therapy after topical therapy. To reflect the population for which etanercept is approved, the company presented sensitivity analyses of different subpopulations.

The CAIN457A2310 study initially had 4 treatment arms to which the children and adolescents were randomly allocated in a 1:1:1:1 ratio. Treatment in the 2 secukinumab arms (referred to as “primary secukinumab arms” by the company because they received secukinumab from the start of the study) and in the placebo arm was double-blind. Treatment with etanercept was blinded only to the assessor of the objective outcomes. After an induction phase of 12 weeks, the children and adolescents in the placebo arm who had not achieved a response according to the Psoriasis Area and Severity Index (PASI) 75 were randomly switched to secukinumab, either at a low dose or at a high dose (referred to by the company as “secondary secukinumab arms”, as they received secukinumab only from week 12). Treatment in the study was to be given in all study arms for 52 weeks (induction phase until week 12, maintenance phase until week 52).

The treatment with secukinumab was not completely in compliance with the Summary of Product Characteristics (SPC). Secukinumab was given as a low and a high dose, but only the dosages in the low-dose secukinumab arms were largely in compliance with the approved dosages. According to the SPC, consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks of treatment with secukinumab. It is not clear from the available documents to what extent treatment discontinuation was considered in patients without response. However, since discontinuation is not mandatory according to the approval, and since at week 16 more than 80% of the patients in the primary secukinumab arms showed a response according to PASI 75, there are no further consequences for the benefit assessment. According to the SPC of etanercept, treatment should be discontinued in patients

who show no response after 12 weeks. Also in this case, it is not clear from the available documents to what extent treatment discontinuation was considered in patients without response. Children and adolescents who respond to the therapy can be treated with etanercept for up to 24 weeks. As described below, treatment with etanercept did not comply with the requirements of the SPC with regard to the procedure for non-response at week 12 and the duration of treatment beyond 24 weeks.

The primary analysis of the study was planned for week 12 and included the comparison of the secukinumab arms with placebo regarding PASI 75 response and Investigator Global Assessment modified 2011 (IGA mod 2011) 0/1 response. Further analyses were conducted at week 24 and week 52. The analysis at week 52 was used by the company in the present dossier for the benefit assessment. Analyses at week 24 are not available.

Study population only partially reflects the approved therapeutic indications of secukinumab and etanercept

Compared with secukinumab, the therapeutic indication of etanercept is narrower. Etanercept is approved for the treatment of chronic severe plaque psoriasis in children and adolescents who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Secukinumab, in contrast, is approved for children and adolescents with moderate to severe plaque psoriasis who are candidates for systemic therapy. Secukinumab thus has a broader approval than etanercept in terms of both disease severity and line of treatment. In accordance with the inclusion criteria, the CAIN457A2310 study also included children and adolescents for whom etanercept is not approved in terms of pretreatment, e.g. those whose plaque psoriasis is insufficiently controlled with topical treatment but who have not yet received systemic therapy or phototherapy. In addition to an analysis of the total population of the study, the company therefore also presented analyses of the subpopulation of patients for whom etanercept is a suitable therapy according to the approval, but in some cases not for all outcomes.

Etanercept treatment not in compliance with SPC requirements

Children and adolescents in the etanercept arm were treated for a period of 52 weeks. According to the SPC of etanercept, however, children and adolescents should only be treated with etanercept for up to 24 weeks. Re-treatment is possible. According to the SPC, treatment should be discontinued in patients who show no response after 12 weeks.

The analyses on the total population of the study at week 12 presented in the European Public Assessment Report (EPAR) show that 33.1% of the children and adolescents in the etanercept arm had not achieved a response according to PASI 75 at this time point; at week 16 this figure was 29.0%, and at week 24 34.4%. At the same time, according to Module 4 E of the dossier, 40 of 41 patients continued treatment with etanercept after completion of the induction phase after 12 weeks. It can be inferred from this that an assessment of the response with corresponding therapeutic consequences was not planned for week 12. Instead, these children and adolescents continued treatment with etanercept beyond week 12, instead of switching to

another, possibly more effective therapy. For this reason alone, the available data from the CAIN457A2310 study are not suitable for answering the present research question of the benefit assessment.

With a treatment duration of 52 weeks, the approved treatment duration of etanercept was exceeded not only in the case of non-response at week 12. According to the approval, treatment of children and adolescents with etanercept should be ended after a total of 24 weeks. Continuation for another 28 weeks not only means that patients without response continued to receive ineffective therapy, but also that patients who had responded well to etanercept received further treatment and were thus exposed to the risk of adverse events (AEs). For example, in relation to the total population of the study, 22.6% of the children and adolescents in the etanercept arm had achieved remission at week 24 (PASI 100), but were treated at an unchanged dose for another 28 weeks, according to the data provided in the EPAR. Overall, all patients continued treatment outside the approval of etanercept after this time point.

Irrespective of the fact that the data of the study are not suitable for the derivation of an added benefit due to the continued therapy with etanercept despite failure to respond after week 12, the results at week 52 presented by the company are not relevant also for this reason alone. Rather, additional analyses of all outcomes at week 24 would be required, especially for the subpopulation of patients for whom etanercept is approved regarding pretreatment.

Further uncertainties

In addition to the use of etanercept in the study, which deviated from the SPC, there are further uncertainties that limit the certainty of results of the CAIN457A2310 study. These result from the administration of secukinumab as a low or high dose, a dosing error in weeks 13 to 15 in the primary secukinumab arms, inconsistent data on protocol violations in the study, and the analyses presented by the company based on the pooling of the primary and secondary secukinumab arms.

Thus, there are no relevant data for the assessment of the added benefit of secukinumab in comparison with the ACT in children and adolescents from the age of 6 years with moderate to severe plaque psoriasis who are candidates for systemic therapy. Hence, there is no hint of an added benefit of secukinumab in comparison with the ACT; an added benefit is therefore not proven.

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

There are no relevant data for the assessment of the added benefit of secukinumab in comparison with the ACT in children and adolescents from the age of 6 years with moderate to severe plaque psoriasis who are candidates for systemic therapy. Hence, an added benefit of secukinumab in comparison with the ACT is not proven.

The result of the assessment of the added benefit of secukinumab in comparison with the ACT is summarized in Table 3.

Table 3: Secukinumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Children and adolescents from the age of 6 years with moderate to severe plaque psoriasis who are candidates for systemic therapy	Adalimumab or **etanercept** or ustekinumab[b]	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. The respective approval of the drugs is to be considered.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of secukinumab in comparison with etanercept as ACT in children and adolescents from the age of 6 years with moderate to severe plaque psoriasis who are candidates for systemic therapy.

Table 4: Research question of the benefit assessment of secukinumab

Therapeutic indication	**ACT**[a]
Children and adolescents from the age of 6 years with moderate to severe plaque psoriasis who are candidates for systemic therapy	Adalimumab or **etanercept** or ustekinumab[b]
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. The respective approval of the drugs is to be considered. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

From the 3 alternatives, the company chose etanercept as ACT.

Etanercept is approved for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Thus, the approved therapeutic indication of etanercept covers only a part of the approved therapeutic indication of secukinumab.

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: 2 July 2020)
- bibliographical literature search on secukinumab (last search on 1 July 2020)
- search in trial registries/trial results databases for studies on secukinumab (last search on 2 July 2020)
- search on the G-BA website for secukinumab (last search on 2 July 2020)

To check the completeness of the study pool:

- search in trial registries for studies on secukinumab (last search on 7 September 2020)

No additional study was identified from the check.

2.3.1 Study included by the company

From the steps of information retrieval mentioned, the company identified the CAIN457A2310 study [3,4] in the relevant therapeutic indication. This RCT is unsuitable for the assessment of the added benefit of secukinumab in comparison with the ACT specified by the G-BA. This is due to the fact that, with regard to the procedure in case of non-response and the duration of treatment, the ACT etanercept was not used in compliance with the SPC in the CAIN457A2310 study. Section 2.3.2 provides a description of the study and a detailed explanation of the reasons why no added benefit can be derived from the available data.

2.3.2 Study characteristics of the study included by the company

Table 5 and Table 6 describe the CAIN457A2310 study included by the company.

Table 5: Characteristics of the study included by the company – RCT, direct comparison: secukinumab vs. etanercept (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CAIN457A2310	RCT, double-blind[b], parallel	Children and adolescents (6 to < 18 years) with severe plaque psoriasis[c] who are candidates for systemic therapy[d]	▪ Secukinumab low dose[e] (N = 40) (primary arm[f]) ▪ secukinumab high dose[g] (N = 40) (primary arm[f]) ▪ etanercept (N = 41) ▪ placebo (N = 41), followed by secukinumab (secondary arms[h]) From these: ▪ subpopulation, etanercept suitable[i], ▫ secukinumab low dose[e] (n = 31) (primary arm[f]) ▫ secukinumab high dose[g] (n = 28) (primary arm[f]) ▫ etanercept (n = 26) ▪ subpopulation, etanercept suitable[i], pooled[j] ▫ secukinumab low dose[e] (n = 39) ▫ secukinumab high dose[g] (n = 42) ▫ etanercept (n = 26) ▪ total population, pooled[j] ▫ secukinumab low dose[e] (n = 56) ▫ secukinumab high dose[g] (n = 58) ▫ etanercept (n = 41)	Screening: 4 weeks Treatment: ▪ induction phase: 12 weeks ▪ maintenance phase: 40 weeks ▪ extension phase[k]: 184 weeks Follow-up: 16 weeks	47 study centres in Belgium, Colombia, Egypt, Estonia, France, Germany, Guatemala, Hungary, Israel, Italy, Japan, Latvia, Poland, Romania, Russia, Spain, Switzerland, USA, United Kingdom 9/2015−ongoing Data cut-off 24 weeks of treatment: 7 March 2019 Data cut-off 52 weeks of treatment: 18 September 2019	Primary: PASI 75 response and IGA mod 2011 0/1 response at week 12 Secondary: mortality, morbidity, health-related quality of life, AEs

Table 5: Characteristics of the study included by the company – RCT, direct comparison: secukinumab vs. etanercept (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. The etanercept arm was single-blind (assessor only).
c. According to the following criteria: PASI score ≥ 20, IGA mod 2011 score = 4 and BSA ≥ 10% at randomization.
d. Classification by the investigator based on the following criteria: inadequate control of symptoms with topical treatment, or failure to respond to or tolerate previous systemic treatment and/or UV therapy.
e. Dosage as specified in the SPC (see also Table 6 on intervention characteristics).
f. Treatment with secukinumab from the start of the study.
g. Higher secukinumab dose than specified in the SPC (see also Table 6 on intervention characteristics).
h. Patients in the placebo arm who had not achieved a PASI 75 response by week 12 received secukinumab at a low or high dose (secondary secukinumab arms) from week 12. 16 patients were allocated to the low-dose secondary treatment arm, and 18 patients to the high-dose secondary arm. The allocation was randomized and conducted in advance at the start of the study. The placebo comparison is not relevant for the assessment and is no longer shown in the following tables.
i. Patients with inadequate response or intolerance to previous systemic therapy or phototherapy in accordance with the SPC of etanercept [5].
j. Data pooling of the primary and secondary secukinumab arms.
k. Treatment in the etanercept arm ended at week 52.

AE: adverse event; BSA: body surface area involvement; IGA mod 2011: Investigator Global Assessment modified 2011; n: relevant subpopulation; N: number of randomized (included) patients; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; UV: ultraviolet; vs.: versus

Table 6: Characteristics of the intervention – RCT, direct comparison: secukinumab vs. etanercept

Study	Intervention	Comparison
CAIN457A2310	Secukinumab, SC, dose based on body weight: ▪ low dose[a] ▫ < 25 kg: 75 mg ▫ ≥ 25 kg to < 50 kg: 75 mg ▫ ≥ 50 kg: 150 mg ▪ high dose ▫ < 25 kg: 75 mg ▫ ≥ 25 kg to < 50 kg: 150 mg ▫ ≥ 50 kg: 300 mg Primary secukinumab arms: ▪ week 0, 1, 2, 3 and 4 secukinumab once per week, then every 4 weeks ▪ week 13, 14 and 15 additional placebo once per week Secondary secukinumab arms[b]: ▪ week 0, 1, 2, 3, 4 and 8 placebo once per week ▪ week 12, 13, 14, 15 and 16 secukinumab once per week, then every 4 weeks	Etanercept, SC, 0.8 mg/kg body weight[c], once per week
	Required pretreatment: ▪ topical therapy ▪ systemic therapy ▪ UV therapy **Non-permitted pretreatment:** ▪ secukinumab or any other biologic drug directly targeting IL-17 or the IL-17 receptor ▪ etanercept **Permitted concomitant treatment:** ▪ emollients without pharmacologically active ingredients and non-drug interventions ▪ only during the screening period: mild or moderate topical corticosteroids for the face, scalp, hands, feet and genitoanal area ▪ from study week 12: topical corticosteroids only for indications other than psoriasis and not on the area affected with psoriasis **Non-permitted concomitant treatment:** ▪ topical applications containing pharmacologically active ingredients such as, for example, lactic acid, salicylic acid, urea, alpha hydroxy acids or fruit acids ▪ other systemic therapies ▪ phototherapy	

a. Dosage as recommended in the SPC.
b. Patients in the placebo arm who had not achieved a PASI 75 response by week 12 received secukinumab at a low or high dose from week 12.
c. Maximum dose: 50 mg

IL-17: interleukin-17; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; SC: subcutaneous; SPC: Summary of Product Characteristics; UV: ultraviolet; vs.: versus

Study design

The CAIN457A2310 study is an RCT comparing 2 different dosages of secukinumab (low dose, high dose) with etanercept and placebo. The study included children and adolescents aged 6 to < 18 years with severe plaque psoriasis. The children and adolescents had to have a history of disease for at least 3 months. The investigator had to consider systemic therapy to be indicated, either because the patients had not responded adequately to topical therapies, systemic therapies or phototherapy, or because they had not tolerated systemic therapies or phototherapy. The severity grade of the psoriasis in the study was defined as a PASI score of ≥ 20, an IGA mod 2011 score of 4, and Body Surface Area (BSA) involvement of ≥ 10%. In terms of the severity of plaque psoriasis, the children and adolescents included in the CAIN457A2310 study represent only part of the population for which secukinumab is approved (moderate to severe plaque psoriasis). The comparator therapy etanercept, on the other hand, is only approved for children and adolescents with severe plaque psoriasis who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies, but not as the first systemic therapy after topical therapy. To reflect the population for which etanercept is approved, the company presented sensitivity analyses of different subpopulations. These are explained in a separate section below.

The inclusion of children and adolescents in the study was carried out in 2 steps. An interim analysis was conducted after about 80 children and adolescents aged 12 to < 18 years had been treated for 28 weeks. On the basis of this analysis, children aged 6 to < 12 years were then also allowed to participate in the study. A total of 162 children and adolescents were included and randomly allocated to the treatment arms, stratified by age (< 12 years/≥ 12 years) and body weight (< 25 kg/≥ 25 kg to < 50 kg/≥ 50 kg).

The CAIN457A2310 study initially had 4 treatment arms to which the children and adolescents were randomly allocated in a 1:1:1:1 ratio. Treatment in the 2 secukinumab arms (referred to as “primary secukinumab arms” by the company because they received secukinumab from the start of the study) and in the placebo arm was double-blind. Treatment with etanercept was blinded only to the assessor of the objective outcomes; the patients and the treating physicians knew the type of treatment.

After an induction phase of 12 weeks, the children and adolescents in the placebo arm who had not achieved a response according to PASI 75 were randomly switched to secukinumab, either at a low dose or at a high dose (referred to by the company as “secondary secukinumab arms”, as they received secukinumab only from week 12). The children and adolescents who had achieved a response according to PASI 75 discontinued the treatment and directly entered the follow-up period. Figure 1 shows a schematic presentation of the study design.

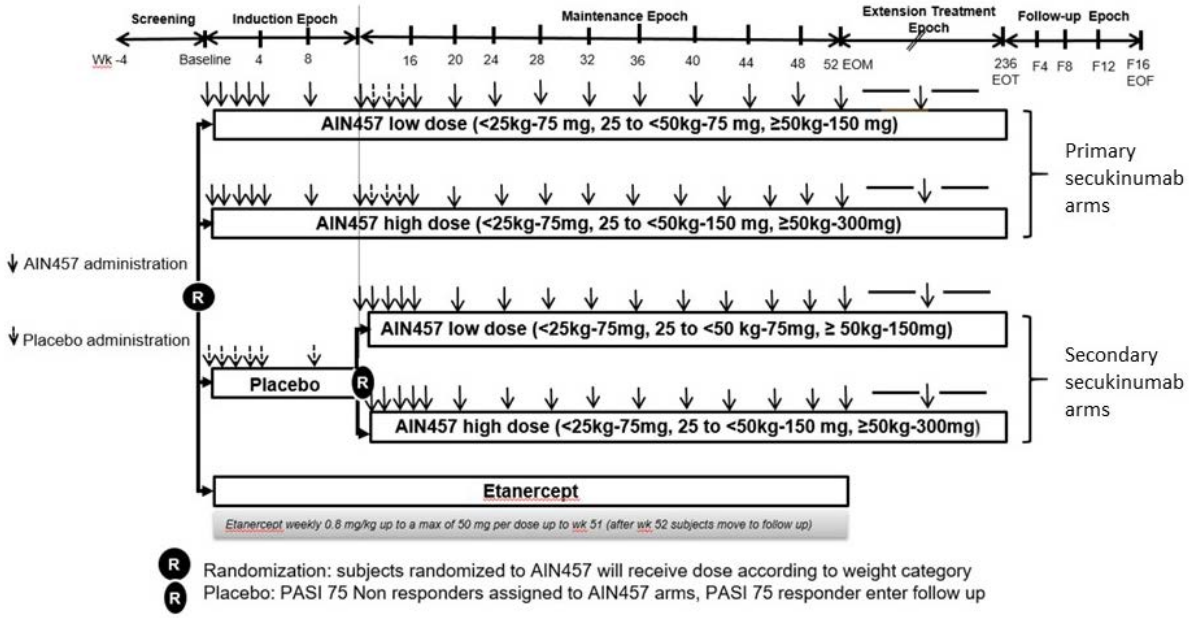

Figure 1: Design of the CAIN457A2310 study (modified adaption of the figure in the EPAR and Module 4 E of the dossier)

Treatment in the study was to be given in all study arms for 52 weeks (induction phase until week 12, maintenance phase until week 52). For the primary and secondary secukinumab arms, treatment was to be continued in an extension phase until week 236. The follow-up period after the end of treatment was planned to be 16 weeks for all study arms.

The treatment with secukinumab was not completely in compliance with the SPC [6]. Secukinumab was given as a low and a high dose, but only the dosages in the low-dose secukinumab arms were largely in compliance with the approved dosages. According to the SPC, consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks of treatment with secukinumab. It is not clear from Module 4 E of the dossier to what extent treatment discontinuation was considered in patients without response. However, since discontinuation is not mandatory according to the approval, and since at week 16 more than 80% of the patients in the primary secukinumab arms showed a response according to PASI 75, there are no further consequences for the benefit assessment. Uncertainties arising from the administration of secukinumab as a low or high dose, as well as from a dosing error in weeks 13 to 15 in the primary secukinumab arms, are discussed below.

According to the SPC of etanercept [5], treatment should be discontinued in patients who show no response after 12 weeks. Children and adolescents who respond to the therapy can be treated with etanercept for up to 24 weeks. As described below, treatment with etanercept did not comply with the requirements of the SPC with regard to the procedure for non-response at week 12 and the duration of treatment beyond 24 weeks.

Emollients without pharmacologically active ingredients and non-drug interventions were allowed as concomitant treatment during the study. Topical corticosteroids were allowed from week 12 onward if they were used for indications other than psoriasis and not on the area affected with psoriasis. The concomitant use of systemic therapies, phototherapy and topical treatments with pharmacologically active ingredients for psoriasis was prohibited.

Coprimary outcomes of the study were PASI 75 response, i.e. an improvement of the psoriasis score by at least 75% compared with baseline, and IGA mod 2011 0/1 response, each at week 12. Patient-relevant secondary outcomes were remission (PASI 100), symptoms, health-related quality of life and side effect outcomes.

The primary analysis of the study was planned for week 12 and included the comparison of the secukinumab arms with placebo regarding the coprimary outcomes mentioned above. Further analyses were conducted at week 24 and week 52. The analysis at week 52 was used by the company in the present dossier for the benefit assessment. The company did not present analyses at week 24 in Module 4 E of its dossier.

Study population only partially reflects the approved therapeutic indications of secukinumab and etanercept

Compared with secukinumab, the therapeutic indication of etanercept is narrower. Etanercept is approved for the treatment of chronic severe plaque psoriasis in children and adolescents who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Secukinumab, in contrast, is approved for children and adolescents with moderate to severe plaque psoriasis who are candidates for systemic therapy. Secukinumab thus has a broader approval than etanercept in terms of both disease severity and line of treatment.

Only children and adolescents with severe plaque psoriasis were included in the CAIN457A2310 study. This means that no comparative data in comparison with the ACT are available from the CAIN457A2310 study for patients with moderate disease. As etanercept is not approved for the treatment of children and adolescents with moderate plaque psoriasis, this population would have to be compared with an ACT option approved for this population.

In accordance with the inclusion criteria, the CAIN457A2310 study also included children and adolescents for whom etanercept is not approved in terms of pretreatment, e.g. those whose plaque psoriasis is insufficiently controlled with topical treatment but who have not yet received systemic therapy or phototherapy. In addition to an analysis of the total population of the study, the company therefore also presented analyses of the subpopulation of patients for whom etanercept is a suitable therapy according to the approval (see section on the analyses presented).

Analyses presented by the company on subpopulations

The company used the total population of the CAIN457A2310 study (referred to by the company as “main analysis”) to derive the added benefit. It additionally presented further

analyses in which the patient population was tailored differently in each case. It referred to them as "sensitivity analyses A, B and C". The company's analyses were based on the populations mentioned below and the comparison of the study arms mentioned. In each case, the low dose (largely compliant with the approval) or the high dose of secukinumab was compared with etanercept:

- Main analysis: total population (primary secukinumab arms versus etanercept arm)
- Sensitivity analysis A: total population (pooled primary and secondary secukinumab arms versus etanercept arm)
- Sensitivity analysis B: population for which etanercept is approved due to the pretreatment (pooled primary and secondary secukinumab arms versus etanercept arm)
- Sensitivity analysis C: population for which etanercept is approved due to the pretreatment (primary secukinumab arms versus etanercept arm), only for side effect outcomes

In its dossier, the company pooled the data from the primary and secondary treatment arms, in each case for the high and low secukinumab dose (referred to by the company as "data pooling"), in 2 analyses (sensitivity analyses A and B of the company). If the analysis includes only those patients who are candidates for etanercept in accordance with the approval, this leads to lower statistical power, which the company tried to compensate for with data pooling. As described above, only those children and adolescents in the secondary secukinumab arms were switched to secukinumab after week 12 who showed no response according to PASI 75 after initial treatment with placebo. The vast majority of patients from the placebo arm continued treatment with secukinumab. However, the pooling of the primary and secondary secukinumab arms produced an uncertainty insofar as secukinumab treatment of the children and adolescents in the secondary secukinumab arms was 12 weeks shorter, and the data from the treatment with placebo were also included in the analyses. This had a potential influence on the results of all outcomes on both the benefit and harm side.

In the present situation, only the subpopulations of the company's sensitivity analyses B and C represent a population approved for both drugs. However, as described above, sensitivity analysis B includes patients from the secondary secukinumab arm who were initially treated with placebo for 12 weeks before starting their active therapy with secukinumab. For the more suitable sensitivity analysis C, however, the company did not provide analyses for all outcomes, but only for the side effect outcomes.

Etanercept treatment not in compliance with SPC requirements

In the etanercept arm, the children and adolescents received a weight-based dose of 0.8 mg etanercept per kg body weight per week (up to a maximum of 50 mg per dose) as a subcutaneous injection for a period of 52 weeks. According to the SPC of etanercept [5], children and adolescents are treated with etanercept for up to 24 weeks. Re-treatment is possible. According to the SPC, treatment should be discontinued in patients who show no response after 12 weeks.

The company did not address in its dossier whether discontinuation of therapy in patients with no response after 12 weeks was planned in the CAIN457A2310 study. In order to estimate how many children and adolescents continued treatment with etanercept despite failure to respond, the response according to PASI 75 can be used. This criterion was also used in the study to operationalize the response at week 12, after patients in the placebo arm were either switched to secukinumab treatment or had to stop treatment. The analyses on the total population of the study at week 12 presented in the EPAR [7] show that 33.1% of the children and adolescents in the etanercept arm had not achieved a response according to PASI 75 at this time point; at week 16 this figure was 29.0%, and at week 24 34.4%. At the same time, according to Module 4 E of the dossier, 40 of 41 patients continued treatment with etanercept after completion of the induction phase after 12 weeks. It can be inferred from this that an assessment of the response with corresponding therapeutic consequences was not planned for week 12. Instead, these children and adolescents continued treatment with etanercept beyond week 12, instead of switching to another, possibly more effective therapy. For this reason alone, the available data from the CAIN457A2310 study are not suitable for answering the present research question of the benefit assessment.

With a treatment duration of 52 weeks, the approved treatment duration of etanercept was exceeded not only in the case of non-response at week 12. According to the approval, treatment of children and adolescents with etanercept should be ended after a total of 24 weeks. Continuation for another 28 weeks not only means that patients without response continued to receive ineffective therapy, but also that patients who had responded well to etanercept received further treatment and were thus exposed to the risk of AEs. For example, in relation to the total population of the study, 22.6% of the children and adolescents in the etanercept arm had achieved remission at week 24 (PASI 100), but were treated at an unchanged dose for another 28 weeks, according to the data provided in the EPAR. Overall, all patients continued treatment outside the approval of etanercept after this time point.

Irrespective of the fact that the data of the study are not suitable for the derivation of an added benefit due to the continued therapy with etanercept despite failure to respond after week 12, the results at week 52 presented by the company are not relevant also for this reason alone. Rather, additional analyses of all outcomes at week 24 would be required, especially for the subpopulation of patients for whom etanercept is approved regarding pretreatment.

Further uncertainties of the CAIN457A2310 study

Treatment with secukinumab

Secukinumab in low or high dose

Children and adolescents in the primary and secondary secukinumab arms received secukinumab as a low or high dose based on their body weight (see Table 6). The dosage in the low-dose treatment arm was largely in compliance with the requirements of the SPC [6]; only the optional increase of the dose to 300 mg in patients with a body weight of ≥ 50 kg was not planned. In the primary and secondary high-dose secukinumab arms, however, children and

adolescents with a body weight of ≥ 25 to < 50 kg received 150 mg, and thus twice the approved dosage, while those with a body weight of ≥ 50 kg received 300 mg. According to the SPC of secukinumab [6], it is only an option for children and adolescents with a body weight of ≥ 50 kg to increase the dose to 300 mg, as some patients may derive additional benefit from the higher dose. It remains unclear for how many children and adolescents this high dose was actually indicated. Conversely, children and adolescents with a body weight of ≥ 50 kg in the low-dose secukinumab arms did not have the option to increase the dose to 300 mg. It cannot be ruled out that an unspecified number of patients with a body weight of ≥ 50 kg would have derived additional benefit from the 300 mg dose.

In summary, treatment in the high-dose secukinumab arms was thus fully compliant with the approval only for children and adolescents with a body weight of < 25 kg, with this stratum representing less than 10% of the patient population in these arms. The results of the primary and secondary high-dose secukinumab arms were therefore subject to uncertainty, as a higher dose can potentially affect the results of all outcomes. In its dossier, the company presented the results separately for the comparison with the low dose of secukinumab and for the comparison with the high dose, but used both comparisons together to derive the added benefit.

Dosing errors in weeks 13, 14 and 15 in the primary secukinumab arms

After the 12-week induction phase, the children and adolescents in the placebo arm who had not achieved a response according to PASI 75 were randomly switched to secukinumab, either at a low dose or at a high dose (secondary secukinumab arms). For this purpose, secukinumab was initially administered once a week, and, after week 16, every 4 weeks, analogous to the induction phase. To maintain blinding, children and adolescents in the 2 primary secukinumab arms were to receive placebo in weeks 13, 14 and 15. According to the company, as a result of a programming error in the interactive response technology (IRT) system, 40% and 50% of patients in the primary secukinumab arms received additional doses of secukinumab in weeks 13, 14 and 15 instead of placebo. In the low-dose secukinumab arm, 16 out of a total of 40 patients, exclusively in the group with a body weight of ≥ 50 kg, were affected. In this group, 3 additional doses of 300 mg secukinumab were given, which was thus twice as high as the 150 mg dose that should be given to children and adolescents with this body weight every 4 weeks. In the high-dose secukinumab arm, 20 of a total of 40 patients were affected. Of these, 5 patients in the group of patients with a body weight of ≥ 25 to < 50 kg received 3 additional doses of 150 mg secukinumab, and 15 patients in the group of patients with a body weight ≥ 50 kg received 3 additional doses of 300 mg secukinumab. According to the EPAR, the dosing error occurred before children aged < 12 years were included in the study.

Inconsistent information on protocol violations

In addition to the dosing error in the primary secukinumab arms described above, other protocol violations, including further deviations from treatment, occurred in the CAIN457A2310 study. The corresponding information for the entire population of the study provided in Module 4 E of the dossier differs from the information in the EPAR. For example, there are deviations in

the data on deviations from the treatment: The EPAR reports deviations from the treatment (excluding treatment deviations due to the dosing error described above) in 30% of the patients in the low-dose secukinumab arm, in 25% of the patients in the high-dose secukinumab arm, and in 44% of the patients in the etanercept arm. In Module 4 E, the company provided markedly lower numbers separately for the induction phase and the maintenance phase. Even when adding up the figures given for the induction and the maintenance phase for patients with at least one protocol deviation (as a rough approximation of the figures for both phases), these discrepancies cannot be resolved for the secukinumab arms. It is unclear whether the dosing error was taken into account or not. A similar situation exists for the overall rate of protocol violations.

Summary

In summary, it can be stated that, in the present situation, only the subpopulations of the company's sensitivity analyses B and C each represent a population approved for both drugs; with the secondary secukinumab arm, sensitivity analysis B also includes patients who initially received placebo for 12 weeks, however. Overall, the available data on the CAIN457A2310 study at week 52 are not relevant, however, as treatment with etanercept in the comparator arm was continued until week 52, although more than 30% of the patients did not show response according to PASI 75 at week 12. For this reason alone, the available data from the CAIN457A2310 study are not suitable for answering the present research question of the benefit assessment. In addition, according to the approval, treatment with etanercept in children and adolescents should be discontinued after 24 weeks. Analyses at week 52 are therefore not relevant for this reason alone. Regardless of the described problems at week 12, this would require analyses of all outcomes at week 24, particularly for the subpopulation of patients for whom etanercept is approved in relation to pretreatment (sensitivity analysis C), possibly in an overall consideration with additional definitions of patient populations.

2.4 Results on added benefit

There are no relevant data for the assessment of the added benefit of secukinumab in comparison with the ACT in children and adolescents from the age of 6 years with moderate to severe plaque psoriasis who are candidates for systemic therapy. Hence, there is no hint of an added benefit of secukinumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

There are no relevant data for the assessment of the added benefit of secukinumab in comparison with the ACT in children and adolescents from the age of 6 years with moderate to severe plaque psoriasis who are candidates for systemic therapy. Hence, an added benefit of secukinumab in comparison with the ACT is not proven.

The result of the assessment of the added benefit of secukinumab in comparison with the ACT is summarized in Table 7.

Table 7: Secukinumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Children and adolescents from the age of 6 years with moderate to severe plaque psoriasis who are candidates for systemic therapy	Adalimumab or **etanercept** or ustekinumab[b]	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. The respective approval of the drugs is to be considered. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit under consideration of the results at week 52 of the study CAIN457A2310.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under https://www.iqwig.de/en/projects/a20-78.html.