IQWiG Reports – Commission No. A20-80

Secukinumab (psoriatic arthritis) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Secukinumab (Psoriasis-Arthritis) – Nutzenbewertung gemäß § 35a SGB V (neue wissenschaftliche Erkenntnisse)* (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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ACT	appropriate comparator therapy
AE	adverse event
bDMARD	biologic disease-modifying anti-rheumatic drug
BSA	body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
DLQI	Dermatology Life Quality Index
DMARD	disease-modifying anti-rheumatic drug
EQ-5D	European Quality of Life-5 Dimensions
FACIT	Functional Assessment of Chronic Illness Therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HAQ-DI	Health Assessment Questionnaire-Disability Index
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDI	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index
MCS	Mental Component Summary
MDA	minimal disease activity
NSAID	nonsteroidal anti-inflammatory drug
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area and Severity Index
PatGA	Patient Global Assessment of Disease Activity
PCS	Physical Component Summary
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
TNF	tumour necrosis factor
VAS	visual analogue scale
VLDA	very low disease activity

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 28 August 2020.

The company submitted a dossier for the early benefit assessment of the drug to be assessed for the first time on 14 December 2015. The company requested a reassessment because of new scientific findings. The reassessment refers to the complete target population in the therapeutic indication: adult patients with active psoriatic arthritis who have responded inadequately to disease-modifying anti-rheumatic drug (DMARD) therapy.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented 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, alone or in combination with methotrexate, in comparison with the appropriate comparator therapy (ACT) in adult patients with active psoriatic arthritis who have responded inadequately to DMARD therapy.

For the present benefit assessment, the research questions presented in Table 2 resulted from the ACTs specified by the GB-A.

Table 2: Research questions of the benefit assessment of secukinumab

Research question	Subindication	ACT[a]
1	Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have responded inadequately to previous DMARD therapy[b, c]	A TNF-alpha antagonist **(adalimumab** or certolizumab pegol or etanercept or golimumab or infliximab) or an IL-17 inhibitor (ixekizumab), possibly in combination with methotrexate
2	Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have responded inadequately to previous bDMARD therapy[b]	Switch to another biologic disease-modifying antirheumatic (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or ustekinumab), possibly in combination with methotrexate

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. According to the G-BA, the patient population considered for research questions 1 and 2 also includes patients who have not tolerated previous DMARD therapy.
c. The patient population considered for research question 1 consists of bDMARD-naive patients.

ACT: appropriate comparator therapy; bDMARD: biologic DMARD; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; IL: interleukin; TNF: tumour necrosis factor

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 for research question 1: biologic disease-modifying antirheumatic drug (bDMARD)-naive patients with active psoriatic arthritis who have responded inadequately to previous DMARD therapy

Study pool and study characteristics

The study pool for the benefit assessment of secukinumab, alone or in combination with methotrexate, in comparison with the ACT consists of the RCT EXCEED.

The EXCEED study is a randomized, double-blind phase 3 study comparing secukinumab (N = 426) with adalimumab (N = 427). The study included adult patients with active psoriatic arthritis, defined according to the Classification Criteria for Psoriatic Arthritis (CASPAR). In addition, the patients had to have at least 3 tender joints out of 78 and at least 3 swollen joints out of 76. Only patients with the diagnosis of active plaque psoriasis, with ≥ 1 psoriatic plaque of ≥ 2 cm diameter, nail changes or a documented history of plaque psoriasis were included.

In the study, secukinumab was used in a dosage of 300 mg by subcutaneous injection. This dosage is only approved for patients with concomitant moderate to severe plaque psoriasis or patients who respond inadequately to tumour necrosis factor (TNF) alpha inhibitors. Thus, secukinumab administration in the EXCEED study was in compliance with the approval only for patients who met these criteria. The administration of adalimumab was in compliance with the approval.

Following the 52-week treatment, the patients were followed up for 16 weeks with regard to side effects.

Primary outcome of the study was the 20% improvement in American College of Rheumatology (ACR) criteria (ACR20). Secondary outcomes were outcomes of the categories of morbidity, health-related quality of life and side effects.

Subpopulation considered

The secukinumab dosage of 300 mg by subcutaneous injection used in the EXCEED study is only approved for patients with concomitant moderate to severe plaque psoriasis or patients who respond inadequately to TNF alpha inhibitors.

The company therefore presented analyses for the subpopulation of patients with concomitant moderate to severe plaque psoriasis; patients who respond inadequately to TNF alpha inhibitors were not included in the study.

The data of the subpopulation (N = 211) presented by the company were used for the present benefit assessment.

Risk of bias

The risk of bias across outcomes was rated as low for the EXCEED study.

The outcome-specific risk of bias was rated as low for the results of each of the following outcomes: enthesitis recorded with the Leeds Enthesitis Index (LEI), dactylitis recorded with the Leeds Dactylitis Index (LDI), health status recorded with the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS), patient-reported global disease activity recorded with the Patient Global Assessment of Disease Activity (PatGA) Psoriatic Arthritis Disease Activity Score (PASDAS), tender/swollen joint count, fatigue recorded with the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), and health-related quality of life recorded with the Short Form (36) Health Survey (SF-36). The outcome-specific risk of bias for the results of each of the other included outcomes was rated as high.

Results

Mortality

All-cause mortality

No death occurred in the EXCEED study during the study period. This resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

Morbidity

Minimal disease activity (MDA), physical functioning (Health Assessment Questionnaire-Disability Index [HAQ-DI]), enthesitis (LEI), dactylitis (LDI), health status (EQ-5D VAS), psoriatic arthritis-related pain (pain VAS), patient-reported global disease activity (PatGA PASDAS VAS), tender joint count, swollen joint count, fatigue (FACIT-Fatigue)

No statistically significant difference between treatment groups was shown for any of the following outcomes: MDA; physical functioning (HAQ-DI), enthesitis (LEI), dactylitis (LDI), health status (EQ-5D VAS), psoriatic arthritis-related pain (pain VAS), patient-reported global disease activity (PatGA PASDAS VAS), tender joint count, swollen joint count, and fatigue (FACIT-Fatigue). In each case, this resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

Skin symptoms (Psoriasis Area and Severity Index [PASI]

For the outcome "skin symptoms" recorded with the PASI 100, a statistically significant difference in favour of secukinumab was shown in comparison with adalimumab. There was an effect modification by the characteristic "age" for this outcome. Overall, there was a hint of an added benefit of secukinumab in comparison with adalimumab for the outcome "skin symptoms" for patients < 65 years of age due to the high risk of bias of the results of this outcome. No usable data were available for patients ≥ 65 years of age. As a result, there was no hint of an added benefit of secukinumab in comparison with adalimumab for this outcome; an added benefit is not proven for this patient group.

Health-related quality of life

SF-36

The Mental Component Summary (MCS) and the Physical Component Summary (PCS) were considered separately for the outcome "health-related quality of life" recorded with the SF-36. In each case, there was no statistically significant difference between the treatment groups for the mean changes. In each case, this resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

Dermatology Life Quality Index (DLQI)

For the outcome "health-related quality of life" recorded with the DLQI, there was no statistically significant difference between the treatment groups for the proportion of patients with DLQI 0 or 1 at the end of the study. This resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs) and discontinuation due to adverse events (AEs)

Based on all events, there was no statistically significant difference between the treatment groups for each of the outcomes "SAEs" and "discontinuation due to AEs". In each case, this

resulted in no hint of lesser or greater harm from secukinumab in comparison with adalimumab; lesser or greater harm is therefore not proven for any of these outcomes.

Infections and infestations

No statistically significant difference between the treatment groups was shown for the outcome "infections and infestations". This resulted in no hint of lesser or greater harm from secukinumab in comparison with adalimumab; lesser or greater harm is therefore not proven.

Results for research question 2: patients with active psoriatic arthritis who have responded inadequately to previous bDMARD therapy

Results

In its dossier, the company presented no data for the assessment of the added benefit of secukinumab, alone or in combination with methotrexate, in comparison with the ACT for patients with active psoriatic arthritis who have responded inadequately to previous bDMARD therapy. This resulted in 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]

On the basis of the results presented, the probability and extent of the added benefit of the drug secukinumab, alone or in combination with methotrexate, in comparison with the ACT are assessed as follows:

Research question 1: bDMARD-naive patients with active psoriatic arthritis who have responded inadequately to previous DMARD therapy

In the overall consideration of the data, there is a positive effect of secukinumab in comparison with adalimumab. This effect is present for adult patients with active psoriatic arthritis aged < 65 years and with concomitant moderate to severe plaque psoriasis for the outcome "skin symptoms (PASI 100)".

In the present situation, the added benefit of secukinumab is therefore based exclusively on an advantage in skin symptoms. However, there are no differences between secukinumab and adalimumab for the outcomes representing arthritis symptoms or for health-related quality of life. Overall, in this data situation, there is a hint of considerable added benefit of secukinumab in comparison with adalimumab for adult bDMARD-naive patients with active psoriatic

[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].

arthritis aged < 65 years and with concomitant moderate to severe plaque psoriasis who have responded inadequately to previous DMARD therapy.

An added benefit of secukinumab in comparison with adalimumab is not proven for adult bDMARD-naive patients with active psoriatic arthritis aged ≥ 65 years and with concomitant moderate to severe plaque psoriasis who have responded inadequately to previous DMARD therapy.

No data are available for the administration of secukinumab in combination with methotrexate.

Research question 2: patients with active psoriatic arthritis who have responded inadequately to previous bDMARD therapy

The company presented no data for the assessment of the added benefit of secukinumab, alone or in combination with methotrexate, in comparison with the ACT for patients with active psoriatic arthritis who have responded inadequately to previous bDMARD therapy. An added benefit of secukinumab, alone or in combination with methotrexate, is not proven for these patients.

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

Table 3: Secukinumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have responded inadequately to previous DMARD therapy[b, c]	A TNF-alpha antagonist **(adalimumab** or certolizumab pegol or etanercept or golimumab or infliximab) or an IL-17 inhibitor (ixekizumab), possibly in combination with methotrexate	Secukinumab alone in patients with concomitant moderate to severe plaque psoriasis: ▪ patients < 65 years: hint of a considerable added benefit[d] ▪ patients ≥ 65 years: added benefit not proven[e] Secukinumab in combination with methotrexate, or in patients without concomitant moderate to severe plaque psoriasis: ▪ Added benefit not proven
2	Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have responded inadequately to previous bDMARD therapy[b]	Switch to another biologic disease-modifying antirheumatic (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or ustekinumab), possibly in combination with methotrexate	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. According to the G-BA, the patient population considered for research questions 1 and 2 also includes patients who have not tolerated previous DMARD therapy.
c. The patient population considered for research question 1 consists of bDMARD-naive patients.
d. The added benefit results solely from an advantage in skin symptoms (PASI 100).
e. Depending on the data constellation, there may also be a lesser benefit of secukinumab.

ACT: appropriate comparator therapy; bDMARD: biologic DMARD; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; IL: interleukin; PASI: Psoriasis Area and Severity Index; TNF: tumour necrosis factor

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of secukinumab, alone or in combination with methotrexate, in comparison with the ACT in adult patients with active psoriatic arthritis who have responded inadequately to DMARD therapy.

For the present benefit assessment, the research questions presented in Table 4 resulted from the ACTs specified by the GB-A.

Table 4: Research questions of the benefit assessment of secukinumab

Research question	Subindication	ACT[a]
1	Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have responded inadequately to previous DMARD therapy[b, c]	A TNF-alpha antagonist **(adalimumab** or certolizumab pegol or etanercept or golimumab or infliximab) or an IL-17 inhibitor (ixekizumab), possibly in combination with methotrexate
2	Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have responded inadequately to previous bDMARD therapy[b]	Switch to another biologic disease-modifying antirheumatic (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or ustekinumab), possibly in combination with methotrexate

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. According to the G-BA, the patient population considered for research questions 1 and 2 also includes patients who have not tolerated previous DMARD therapy.
c. The patient population considered for research question 1 consists of bDMARD-naive patients.

ACT: appropriate comparator therapy; bDMARD: biologic DMARD; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; IL: interleukin; TNF: tumour necrosis factor

In the present assessment, the following terms are used for the patient populations of the 2 research questions:

- Research question 1: bDMARD-naive patients with active psoriatic arthritis who have responded inadequately to previous DMARD therapy
- Research question 2: patients with active psoriatic arthritis who have responded inadequately to previous bDMARD therapy

In accordance with the G-BA, the patient population considered for research questions 1 and 2 includes not only patients who have responded inadequately to DMARD therapy, but also patients who have not tolerated previous DMARD therapy.

The company followed the specification of the ACT for both research questions. For research question 1, the company chose adalimumab from the specified options. For research question 2, the company did not choose any of the ACTs presented. It stated that there was no evidence to

demonstrate an added benefit in comparison with any of the specified ACTs for this research question.

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 Research question 1: bDMARD-naive patients with active psoriatic arthritis who have responded inadequately to previous DMARD 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 list on secukinumab (status: 14 August 2020)
- bibliographical literature search on secukinumab (last search on 16 June 2020)
- search in trial registries/trial results databases for studies on secukinumab (last search on 17 June 2020)
- search on the G-BA website for secukinumab (last search on 17 June 2020)

To check the completeness of the study pool:

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

The check did not identify any additional relevant studies.

2.3.1.1 Study included

The study listed in the following table was included in the benefit assessment.

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

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
CAIN457F2366 (EXCEED[c])	No	Yes	No	No[d]	Yes [3,4]	Yes [5]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.
d. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

CSR: clinical study report; RCT: randomized controlled trial; vs.: versus

The study pool for the benefit assessment of secukinumab, alone or in combination with methotrexate, in comparison with the ACT consists of the RCT EXCEED, and concurs with the study pool of the company.

2.3.1.2 Study characteristics

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
EXCEED	RCT, double-blind, parallel	Adult patients with active psoriatic arthritis[b]: ▪ inadequate control of symptoms under NSAIDs ≥ 4 weeks prior to randomization or NSAID intolerance, and ▪ inadequate response under a csDMARD or discontinuation of csDMARD therapy due to intolerance, and ▪ no previous bDMARD therapy for the treatment of psoriatic arthritis or psoriasis	Secukinumab (N = 426) adalimumab (N = 427) Considered subpopulation thereof[c] (for research question 1): secukinumab (n = 110) adalimumab (n = 101)	Screening: 8 weeks Treatment: 52 weeks Follow-up: 16 weeks for AEs[d] 4/2017–12/2019	161 centres in: Australia, Bulgaria, Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, India, Israel, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Russia, Slovakia, South Korea, Spain, United Kingdom, USA	Primary: ACR20 at week 52 Secondary: morbidity, health-related quality of life, AEs

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. Psoriatic arthritis defined according to CASPAR criteria; symptoms for at least 6 months; in addition, the patients had to have at least 3 tender joints out of 78 and at least 3 swollen joints out of 76, and a diagnosis of active plaque psoriasis, with ≥ 1 psoriatic plaque of ≥ 2 cm diameter or nail changes or a documented history of plaque psoriasis.
c. Patients with concomitant moderate to severe plaque psoriasis (see Section 2.3.1.2).
d. It is not clear from the information in Module 4 B whether all other outcomes were also followed up.

ACR: American College of Rheumatology; AE: adverse event; bDMARD: biologic DMARD; CASPAR: Classification Criteria for Psoriatic Arthritis; csDMARD: conventional synthetic DMARD; DMARD: disease-modifying antirheumatic drug; n: relevant subpopulation; N: number of randomized patients; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: secukinumab vs. adalimumab

Study	Intervention	Comparison
EXCEED	Secukinumab 300 mg, SC weeks 0–4: once per week weeks 5–52: once every 4 weeks (week 8, 12, 16 etc., last dose in week 48) + adalimumab placebo SC every 4 weeks (week 6, 10, 14 etc.) until week 50	Adalimumab 40 mg, SC weeks 0–50: once every 2 weeks (week 0, 2, 4 etc., last dose in week 50) + secukinumab placebo in weeks 1 and 3
	Pretreatment not allowed: ▪ biologic drugs for the treatment of psoriatic arthritis or psoriasis[a] ▪ cell-depleting therapies (e.g. alemtuzumab) ▪ intramuscular, intravenous, intraarticular corticosteroid therapy within 4 weeks before randomization ▪ opioid analgesics (e.g. methadone, hydromorphone, morphine) **Concomitant treatment** not allowed: ▪ continuation of previous csDMARD therapy[b] ▪ topical corticosteroids or phototherapy (UVA, UVB from 2 weeks before randomization, PUVA from 4 weeks before randomization) or oral or topical retinoids (from 4 weeks before randomization) for the treatment of psoriasis allowed: ▪ continuation of previous NSAID therapy at a stable dose since 2 weeks before randomization until week 52 ▪ continuation of previous corticosteroid therapy (up to 10 mg prednisone or equivalent per day) in a stable dose[c] since 2 weeks before randomization until week 52 ▪ emergency treatment (e.g. csDMARDs)	

a. TNF-alpha inhibitors, secukinumab or any other biologic drug targeting IL-17 or IL-17 receptor
b. Patients had to have discontinued their csDMARD therapy 4 weeks before randomization (for leflunomide: 8 weeks before randomization, unless a colestyramine washout was performed).
c. According to the company, a dose adjustment was possible in principle, if medically indicated.

csDMARD: conventional synthetic disease-modifying antirheumatic drug; IL: interleukin; NSAID: nonsteroidal anti-inflammatory drug; PUVA: psoralen and UVA (photochemotherapy); RCT: randomized controlled trial; SC: subcutaneous; TNF: tumour necrosis factor; UVA: ultraviolet A radiation; UVB: ultraviolet B radiation; vs.: versus

Study design

The EXCEED study is a randomized, double-blind phase 3 study comparing secukinumab with adalimumab. The study included adult patients with active psoriatic arthritis, defined according to the CASPAR criteria [6]. In addition, the patients had to have at least 3 tender joints out of 78 and at least 3 swollen joints out of 76. Only patients with the diagnosis of active plaque psoriasis, with ≥ 1 psoriatic plaque of ≥ 2 cm diameter, nail changes or a documented history of plaque psoriasis were included. The symptoms of psoriatic arthritis had to be inadequately controlled for at least 6 months before the start of the study despite previous treatment with

nonsteroidal anti-inflammatory drugs (NSAIDs). In addition, patients either had to have an inadequate response to previous csDMARD therapy or have discontinued this therapy due to intolerance. Therapy with a biological (b)DMARD for the treatment of psoriatic arthritis or psoriasis before the start of the study was not allowed, however.

A total of 853 patients were randomly assigned to 52 weeks of treatment with secukinumab (300 mg per dose; N = 426) or adalimumab (40 mg per dose; N = 427), each as monotherapy. The administration of the combination therapy of secukinumab with methotrexate, which is also comprised by the approval [7], was not planned in the study.

In the study, secukinumab was used in a dosage of 300 mg by subcutaneous injection. This dosage is only approved for patients with concomitant moderate to severe plaque psoriasis or patients who respond inadequately to TNF alpha inhibitors. Thus, secukinumab administration in the EXCEED study was in compliance with the approval only for patients who met these criteria. For all other patients, the recommended dose is 150 mg by subcutaneous injection according to the Summary of Product Characteristics (SPC) [7]. The administration of adalimumab was in compliance with the approval [8].

During the study, patients had to continue their NSAID therapy and remain on the stable dose they had been taking since 2 weeks before randomization. According to information provided in Module 4 B, administration of an unchanged dosage was also planned for corticosteroids; however, according to the information provided by the company, a dose adjustment of a corticosteroid therapy initiated before the start of the study was possible in principle, if medically indicated.

Following the 52-week treatment, the patients were followed up for 16 weeks with regard to side effects.

Primary outcome of the study was ACR20 improvement. Secondary outcomes were outcomes of the categories of morbidity, health-related quality of life and side effects.

Subpopulation considered for research question 1

The secukinumab dosage of 300 mg by subcutaneous injection used in the EXCEED study is only approved for patients with concomitant moderate to severe plaque psoriasis or patients who respond inadequately to TNF alpha inhibitors.

The company therefore presented analyses for the subpopulation of patients with concomitant moderate to severe plaque psoriasis; patients who respond inadequately to TNF alpha inhibitors were not included in the study.

The company defined the presence of moderate to severe plaque psoriasis on the basis of the 2 criteria Body Surface Area (BSA) > 10% and/or PASI ≥ 10. In total, the company thus considered 211 (24.7%) of the total of 853 patients (secukinumab arm: N = 110; adalimumab

arm: N = 101). The severity definition provided by the company is to be regarded as a sufficient representation of moderate to severe psoriasis.

The data of the subpopulation presented by the company were used for the present benefit assessment. The company presented no data for patients without concomitant moderate to severe plaque psoriasis.

Table 8 shows the characteristics of the patients in the subpopulation of the included study considered for the benefit assessment.

Table 8: Characteristics of the study populations – RCT, direct comparison: secukinumab vs. adalimumab (multipage table)

Study Characteristic Category	Secukinumab N = 110	Adalimumab N = 101
EXCEED		
Age [years], mean (SD)	49 (12)	47 (12)
Sex [F/M], %	40/60	44/56
Family origin, n (%)		
Asian	2 (1.8)	7 (6.9)
Indigenous peoples of the Americas	0 (0)	1 (1.0)
Black	0 (0)	2 (2.0)
Caucasian	108 (98.2)	90 (89.1)
Other	0 (0)	1 (1.0)
Region, n (%)		
America	0 (0)	5 (5.0)
Asia	4 (3.6)	8 (7.9)
Australia	1 (0.9)	3 (3.0)
Europe	105 (95.5)	85 (84.2)
Time since first diagnosis [years], mean (SD)	6.1 (8.9)	6.7 (8.4)
Enthesitis (LEI), n (%)	59 (53.6)	69 (68.3)
Dactylitis, n (%)	35 (31.8)	33 (32.7)
PASI, mean (SD)	16.2 (9.6)	15.0 (8.9)
BSA, mean (SD)	24.5 (15.7)	24.2 (16.3)
DAS28, mean (SD)	4.7 (0.9)	4.8 (1.0)
Smoker, n (%)	29 (26.4)	25 (24.8)
Previous documented treatment		
DMARD[a], n (%)	107 (97.3)	96 (95.0)
Methotrexate, n (%)	92 (86.0[b])	87 (90.6[b])
TNF alpha antagonists, n (%)	0 (0)	0 (0)
Discontinuation of DMARDs due to lack of efficacy, n (%)	66 (61.7[b])	62 (64.6[b])[c]
Discontinuation of DMARDs due to lack of tolerability, n (%)	41 (38.3[b])	42 (43.8[b])[c]
Treatment discontinuation, n (%)	6 (5.5)	18 (17.8)
Study discontinuation, n (%)	6 (5.5)	17 (16.8)

a. According to the company, DMARDs are classified as csDMARDs, bDMARDs, apremilast or tofacitinib. In the EXCEED study, previous bDMARD treatment was not allowed.
b. Institute's calculation; based on the number of patients with documented previous DMARD treatment.
c. According to Module 4 B, the documented number of patients who discontinued DMARD therapy before the study due to lack of efficacy or lack of tolerability (N = 104) exceeds the number of patients for whom previous DMARD treatment was documented (N = 96). There is no information in Module 4 B to explain this discrepancy.

Table 8: Characteristics of the study populations – RCT, direct comparison: secukinumab vs. adalimumab (multipage table)

Study Characteristic Category	Secukinumab N = 110	Adalimumab N = 101
BSA: body surface area; csDMARD: conventional synthetic DMARD; bDMARD: biologic DMARD; DAS28: Disease Activity Score 28; DMARD: disease-modifying antirheumatic drug; F: female; LEI: Leeds Enthesitis Index; M: male; n: number of patients in the category; N: number of randomized patients; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; SD: standard deviation; TNF: tumour necrosis factor; vs.: versus		

Patient characteristics were sufficiently similar between the treatment groups. The mean age of the patients was about 48 years, and most of them were male. Almost all patients had previously been treated with a DMARD, mainly methotrexate. About 60% of the patients discontinued their previous therapy due to lack of efficacy, the remaining patients due to lack of tolerability.

However, there were differences between the 2 treatment arms in the number of patients with enthesitis (intervention arm: 53.6%, comparator arm: 68.3%). However, these differences do not call into question the similarity of the subpopulations. In addition, markedly more patients discontinued their therapy or the study in the comparator arm than in the intervention arm (about 17% compared with 6%).

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: secukinumab vs. adalimumab

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
EXCEED	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for the EXCEED study. This concurs with the company's assessment.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - MDA
  - physical functioning (HAQ-DI)
  - enthesitis (LEI)
  - dactylitis (LDI)
  - skin symptoms (PASI)
  - health status (EQ-5D VAS)
  - psoriatic arthritis-related pain (pain VAS)
  - patient-reported global disease activity (PatGA PASDAS VAS)
  - tender/swollen joint count
  - fatigue (FACIT-Fatigue)
- Health-related quality of life
  - generic health-related quality of life (SF-36)
  - disease-specific health-related quality of life (DLQI)
- Side effects
  - SAEs
  - discontinuation due to AEs
  - infections and infestations
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 B).

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

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

Study	Outcomes															
	All-cause mortality	**MDA**	**Physical functioning (HAQ-DI)**	**Enthesitis (LEI)**	**Dactylitis (LDI)**	**Skin symptoms (PASI)**	**Health status (EQ-5D VAS)**	**Psoriatic arthritis-related pain (pain VAS)**	**Patient-reported global disease activity (PatGA PASDAS VAS)**	**Tender/swollen joint count**	**Fatigue (FACIT-Fatigue)**	**Health-related quality of life (SF-36)**	**Health-related quality of life (DLQI)**	**SAEs**	**Discontinuation due to AEs**	**Infections and infestations (SOC, AE)**
EXCEED	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

AE: adverse event; DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ-DI: Health Assessment Questionnaire-Disability Index; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesitis Index; MDA: minimal disease activity; PASDAS: Psoriatic Arthritis Disease Activity Score; PASI: Psoriasis Area and Severity Index; PatGA: Patient Global Assessment of Disease Activity; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

Morbidity

Patient-reported global disease activity

The company presented analyses on the patient-reported global disease activity recorded with 2 different VAS (PatGA VAS and PatGA PASDAS VAS). Both instruments enquire about the effects of psoriasis or psoriatic arthritis on the patients. The question addressed to the patients is similar in both instruments. Differences exist in the time periods to be considered by the patients for answering the questions (PatGA VAS: current day; PatGA PASDAS VAS: past week). Both instruments are suitable for representing the disease activity of the patients.

The benefit assessment considered the results of the PatGA PASDAS VAS because, in contrast to the PatGA VAS, higher response rates were available in the present data constellation and, unlike the PatGA VAS, this resulted in a low risk of bias. In addition, this operationalization includes information from a longer period of time considered by the patients. However, the conclusions from the results obtained using the PatGA VAS do not differ from the results obtained using the PatGA PASDAS VAS.

Outcomes additionally presented

In addition to the patient-relevant outcomes, the following outcomes are presented as supplementary information, but were not taken into account for the derivation of the added benefit:

- Skin symptoms (PASI 90 or PASI 75)

Information on the extent and severity of skin symptoms of redness, thickness and scaling on different parts of the body is included in the analysis of the PASI. This information is summarized into a single total value. Due to such integration of the values, the final PASI score alone does not give precise information about the localization of the affected body parts. This is important for the assessment of the patient-relevant treatment success of psoriasis therapy, as even with a reduction of the PASI score, symptom manifestations may remain on various body parts, such as the head or genital area, which patients perceive as particularly impairing. Due to the design of the instrument, analyses on PASI 90 or PASI 75 therefore do not allow any conclusions to be drawn about how burdensome the remaining symptoms are for the patients.

- Very low disease activity (VLDA)

VLDA was operationalized in the EXCEED study as fulfilment of all 7 criteria included in the MDA. The MDA includes the most important outcomes relevant to psoriatic arthritis. A fulfilment of 5 of the 7 criteria is suitable to represent the treatment goal of low disease activity [9]. It is unclear what significance the VLDA has in comparison with the MDA. The VLDA is presented as supplementary information.

Note on responder analyses of the outcomes "physical functioning (HAQ-DI)", "fatigue (FACIT-Fatigue)" and "health-related quality of life (SF-36)"

The company presented different responder analyses in its dossier:

- Physical functioning (HAQ-DI): proportion of patients with an improvement of ≥ 0.35 points
- Fatigue (FACIT-Fatigue): proportion of patients with an improvement of ≥ 4 points
- Health-related quality of life (SF-36): proportion of patients with an improvement of ≥ 2.5 points or by ≥ 5 points

These responder analyses were not used for the dossier assessment. As explained in the General Methods of the Institute [1];Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2020 #106}, for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range).

In each case, the analyses of the mean change at the end of the study were used for the outcomes. The responder analyses on physical functioning (HAQ-DI) presented by the company are presented as supplementary information in Appendix A of the full dossier assessment because this response criterion was used in previous assessments in the therapeutic indication of psoriatic arthritis [10,11].

2.3.2.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: secukinumab vs. adalimumab

Study	Study level	Outcomes															
		All-cause mortality	MDA	Physical functioning (HAQ-DI)	Enthesitis (LEI)	Dactylitis (LDI)	Skin symptoms (PASI)	Health status (EQ-5D VAS)	Psoriatic arthritis-related pain (pain VAS)	Patient-reported global disease activity (PatGA PASDAS VAS)	Tender/swollen joint count	Fatigue (FACIT-Fatigue)	Health-related quality of life (SF-36)	Health-related quality of life (DLQI)	SAEs	Discontinuation due to AEs	Infections and infestations (SOC, AE)
EXCEED	L	H[a]	H[b, c]	H[d]	L	L	H[b]	L	H[d]	L	L	L	L	H[b]	H[a]	H[a]	H[a]

a. Incomplete observations for potentially informative reasons. High proportion (all-cause mortality) or possibly high proportion (AEs) of patients not fully considered in the analysis (> 10%), or large difference between the treatment groups (> 5 percentage points) in the proportion of patients not fully considered in the analysis.
b. Missing information on the variables used for multiple imputation. Missing data on the number of responders actually observed in week 52.
c. Outcome is composed of outcomes with results with high risk of bias.
d. Differing response rates to questionnaires between the treatment arms in the course of the study.

AE: adverse event; DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; H: high; HAQ-DI: Health Assessment Questionnaire-Disability Index; L: low; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesitis Index; MDA: minimal disease activity; PASDAS: Psoriatic Arthritis Disease Activity Score; PASI: Psoriasis Area and Severity Index; PatGA: Patient Global Assessment of Disease Activity; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The high risk of bias for the result of the outcome "all-cause mortality" was due to incomplete observations for potentially informative reasons (study discontinuations: secukinumab arm [5.5%] versus adalimumab arm [16.8%]). This resulted in a high proportion of patients not fully considered in the analysis, or in a large difference between the treatment groups in the proportion of patients not fully considered in the analysis. This deviates from the assessment of the company, which rated the risk of bias of the results for the outcome "all-cause mortality" as low.

The risk of bias was rated as high for the results of the outcomes "MDA", "skin symptoms (PASI)", and "health-related quality of life (DLQI)". This was due to missing information on the variables used for multiple imputation and missing information on the number of responders actually observed in week 52. For the outcome "MDA", there was the additional fact that results from other outcomes with results with potential high risk of bias were included in this outcome. This deviates from the assessment of the company, which rated the risk of bias of these outcomes as low in each case.

The risk of bias was also rated as high for the results of the outcomes "physical functioning (HAQ-DI)" and "psoriatic arthritis-related pain (pain VAS)". This was due to the differing response rates to questionnaires between the treatment arms in the course of the study. This concurs with the company's assessment.

For the results of the outcomes of the outcome category "side effect", the high risk of bias was due to incomplete observations for potentially informative reasons (study discontinuations). This resulted in a possibly high proportion of patients not fully considered in the analysis, or in a large difference between the treatment groups in the proportion of patients not fully considered in the analysis. This deviates from the assessment of the company, which rated the risk of bias of the results for the outcomes of the category of side effects as low.

Transferability of the study results to the German health care context

The company stated that the subpopulation presented in the dossier largely showed structural equality compared with the patient population with psoriatic arthritis in Germany with regard to its demographic and other characteristics at baseline, in the diagnosis and in the concomitant therapy. According to the company, the study results on the subpopulation were thus transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.3.2.3 Results

Table 12 and Table 13 summarize the results on the comparison of secukinumab with adalimumab in bDMARD-naive patients with active psoriatic arthritis and concomitant moderate to severe plaque psoriasis who have responded inadequately to or have not tolerated

previous DMARD therapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The results on common AEs and AEs that led to treatment discontinuation are presented in Appendix B of the full dossier assessment. The common SAEs are not listed because there were no events at System Organ Class (SOC)/Preferred Term (PT) level that met the criteria for presentation (see explanation in Appendix B of the full dossier assessment).

Table 12: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: secukinumab vs. adalimumab (multipage table)

Study Outcome category Outcome	Secukinumab		Adalimumab		Secukinumab vs. adalimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
EXCEED					
Mortality					
All-cause mortality	110	0 (0)	101	0 (0)	–
Morbidity					
Minimal disease activity (MDA)[a]	110	51.0[b] (46.4)	101	39.9[b] (39.5)	1.17 [0.85; 1.62]; 0.325[c]
Very low disease activity (VLDA, supplementary information)[a]	*110*	*16.3[b] (14.8)*	*101*	*15.9[b] (15.7)*	*0.94 [0.49; 1.80]; 0.855[c]*
Skin symptoms					
PASI 100	110	43.8[b] (39.8)	101	24.5[b] (24.3)	1.64 [1.08; 2.50]; 0.021[c]
PASI 90 (supplementary information)	*110*	*78.0[b] (70.9)*	*101*	*45.9[b] (45.4)*	*1.56 [1.21; 2.01]; < 0.001[c]*
PASI 75 (supplementary information)	*110*	*98.4[b] (89.5)*	*101*	*67.4[b] (66.7)*	*1.34 [1.14; 1.57]; < 0.001[c]*
Health-related quality of life					
DLQI (0 or 1)	110	56.2[b] (51.1)	101	40.3[b] (39.9)	1.28 [0.94; 1.75]; 0.118[c]
Side effects					
AEs (supplementary information)	110	74 (67.3)	101	71 (70.3)	–
SAEs	110	7 (6.4)	101	7 (6.9)	0.92 [0.33; 2.53]; 0.869
Discontinuation due to AEs	110	1 (0.9)	101	3 (3.0)	0.31 [0.03; 2.90]; 0.302
Infections and infestations (SOC, AE)	110	62 (56.4)	101	48 (47.5)	1.19 [0.91; 1.54]; 0.203

a. For classification as an MDA responder, 5 of the following 7 criteria must be met; for classification as a VLDA responder, 7 of the 7 criteria must be met: tender joint count based on 78 joints ≤ 1; swollen joint count based on 76 joints ≤ 1; PASI score ≤ 1 or BSA ≤ 3%; pain (VAS) ≤ 15 mm; patient-reported global disease activity (PatGA VAS) ≤ 20 mm; HAQ-DI score (physical functioning) ≤ 0.5; LEI score (enthesitis) ≤ 1.
b. Due to the multiple imputation of missing values, there is usually no whole number of patients with event.
c. Combining of RR, 95% CI and p-value across all imputation data sets using Rubin's rule.

AE: adverse event; BSA: body surface area; CI: confidence interval; DLQI: Dermatology Life Quality Index; HAQ-DI: Health Assessment Questionnaire-Disability Index; LEI: Leeds Enthesitis Index; MDA: minimal disease activity; n: number of patients with (at least one) event; N: number of analysed patients; PASI: Psoriasis Area and Severity Index; PatGA: Patient Global Assessment of Disease Activity; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; VLDA: very low disease activity; vs.: versus

Table 13: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: secukinumab vs. adalimumab (multipage table)

Study Outcome category Outcome	Secukinumab			Adalimumab			Secukinumab vs. adalimumab
	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	MD [95% CI]; p-value[b]
EXCEED							
Morbidity							
Physical functioning (HAQ-DI)[c]	110	1.26 (0.63)	−0.60 (0.05)	101	1.32 (0.69)	−0.56 (0.05)	−0.05 [−0.19; 0.09]; 0.517
Enthesitis (LEI)[c]	110	1.31 (1.49)	−1.14 (0.09)	100	2.00 (1.93)	−1.21 (0.10)	0.07 [−0.21; 0.35]; 0.620
Dactylitis (LDI)[c]	110	17.64 (49.52)	−19.72 (0.51)	100	19.62 (58.36)	−18.88 (0.56)	−0.85 [−2.34; 0.65]; 0.267
Health status (EQ-5D VAS)[d]	110	46.45 (21.80)	20.31 (1.93)	99	46.50 (21.28)	22.57 (2.14)	−2.26 [−7.95; 3.42]; 0.433
Psoriatic arthritis-related pain (pain VAS)[c]	110	57.89 (25.01)	−31.64 (2.07)	100	59.71 (24.00)	−30.32 (2.27)	−1.32 [−7.37; 4.73]; 0.667
Patient-reported global disease activity (PatGA PASDAS VAS)[c]	110	70.65 (19.23)	−38.70 (2.25)	100	69.18 (19.53)	−38.14 (2.47)	−0.56 [−7.16; 6.03]; 0.866
Tender joint count[c, e]	110	17.40 (9.96)	−14.92 (0.51)	100	19.70 (12.54)	−14.48 (0.56)	−0.44 [−1.94; 1.06]; 0.564
Swollen joint count[c e]	110	9.27 (6.53)	−8.77 (0.24)	100	10.69 (8.16)	−8.60 (0.26)	−0.17 [−0.87; 0.52]; 0.621
Fatigue (FACIT-Fatigue)[d]	110	28.90 (11.36)	8.82 (0.90)	99	28.96 (10.69)	6.82 (0.98)	2.00 [−0.63; 4.62]; 0.135
Health-related quality of life							
SF-36[d]							
Physical Component Summary (PCS)	110	36.81 (7.50)	8.17 (0.74)	99	36.22 (8.98)	7.62 (0.81)	0.55 [−1.60; 2.70]; 0.612
Mental Component Summary (MCS)	110	40.17 (12.03)	7.62 (0.92)	99	41.74 (10.57)	5.32 (1.02)	2.30 [−0.41; 5.01]; 0.096
Physical functioning	110	42.09 (24.57)	23.72 (2.20)	99	40.50 (26.90)	21.08 (2.40)	2.64 [−3.78; 9.07]
Physical role functioning	110	42.84 (24.31)	23.80 (2.18)	99	45.67 (25.15)	19.14 (2.40)	4.66 [−1.74; 11.07]
Bodily pain	110	34.85 (20.05)	26.49 (2.11)	99	34.87 (19.70)	23.00 (2.35)	3.49 [−2.73; 9.72]
General health perception	110	40.48 (17.56)	11.90 (1.68)	99	39.53 (17.96)	11.99 (1.83)	−0.10 [−4.99; 4.80]
Vitality	110	36.93 (20.56)	17.37 (1.89)	99	39.17 (20.76)	12.30 (2.08)	5.07 [−0.48; 10.63]
Social functioning	110	56.25 (28.62)	23.51 (2.19)	99	55.82 (25.22)	18.19 (2.42)	5.32 [−1.13; 11.76]

Table 13: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: secukinumab vs. adalimumab (multipage table)

Study Outcome category Outcome	Secukinumab			Adalimumab			Secukinumab vs. adalimumab
	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	MD [95% CI]; p-value[b]
Emotional role functioning	110	58.49 (28.42)	19.58 (2.15)	99	60.40 (24.56)	15.47 (2.39)	4.11 [−2.24; 10.45]
Mental wellbeing	110	50.18 (22.49)	15.62 (1.82)	99	54.26 (21.75)	10.95 (2.01)	4.67 [−0.69; 10.03]

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b. MMRM analysis of the ITT population with the variables treatment arm, visit, weight, baseline value, interaction term treatment arm and visit, and interaction term baseline value and visit.
c. Lower (decreasing) values indicate an improvement of symptoms; negative effects (secukinumab minus adalimumab) indicate an advantage for secukinumab.
d. Higher (increasing) values indicate an improvement of symptoms or quality of life; positive effects (secukinumab minus adalimumab) indicate an advantage for secukinumab.
e. Tender joint count based on 78 joints, and swollen joint count based on 76 joints.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ-DI: Health Assessment Questionnaire-Disability Index; ITT: intention to treat; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesitis Index; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; PASDAS: Psoriatic Arthritis Disease Activity Score; PatGA: Patient Global Assessment of Disease Activity; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SF-36: Short Form (36) Health Survey; VAS: visual analogue scale; vs.: versus

On the basis of the available data, at most indications of an added benefit can be determined for the following outcomes: enthesitis, dactylitis, health status recorded with the EQ-5D VAS, patient-reported global disease activity recorded with the PatGA PASDAS VAS, tender/ swollen joint count, fatigue recorded with the FACIT-Fatigue, and health-related quality of life recorded with the SF-36; and at most hints, e.g. of an added benefit, for all other outcomes due to the high risk of bias.

Mortality

All-cause mortality

No death occurred in the EXCEED study during the study period. This resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

MDA

There was no statistically significant difference between the treatment groups for the outcome "MDA". This resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Physical functioning (HAQ-DI)

For the outcome "physical functioning" recorded with the HAQ-DI, no statistically significant difference between the treatment groups was shown for the mean change. This resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

This corresponds to the assessment of the company, which presented further additional operationalizations for this outcome (proportion of patients with an improvement of ≥ 0.3 or ≥ 0.35) and also did not derive an added benefit on the basis of these analyses.

Enthesitis (LEI)

For the outcome "enthesitis" recorded with the LEI, no statistically significant difference between the treatment groups was shown for the mean change. This resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

This corresponds to the assessment of the company, which additionally considered the proportion of patients with presence of enthesitis at the end of the study and also did not derive an added benefit on the basis of this analysis.

Dactylitis (LDI)

For the outcome "dactylitis" recorded with the LDI, no statistically significant difference between the treatment groups was shown for the mean change. This resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

This corresponds to the assessment of the company, which additionally considered the proportion of patients with presence of dactylitis at the end of the study and also did not derive an added benefit on the basis of this analysis.

Skin symptoms (PASI)

For the outcome "skin symptoms" recorded with the PASI 100, a statistically significant difference in favour of secukinumab was shown in comparison with adalimumab. An effect modification by the characteristic "age" was shown for this outcome (see Section 2.3.2.4). Overall, there was a hint of an added benefit of secukinumab in comparison with adalimumab

for the outcome "skin symptoms" for patients < 65 years of age due to the high risk of bias of the results of this outcome. There were no usable data for patients ≥ 65 years of age (see Section 2.3.2.4). As a result, there was no hint of an added benefit of secukinumab in comparison with adalimumab for this outcome; an added benefit is not proven for this patient group.

This deviates from the approach of the company insofar as the company considered no effect modifications in the derivation of the added benefit. On the basis of the subpopulation considered, it also determined an added benefit of secukinumab, but made no statement on probability.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for the outcome "health status" recorded with the EQ-5D VAS. This resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Psoriatic arthritis-related pain (pain VAS)

There was no statistically significant difference between the treatment groups for the outcome "psoriatic arthritis-related pain" recorded with the VAS. This resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Patient-reported global disease activity (PatGA PASDAS VAS)

There was no statistically significant difference between the treatment groups for the outcome "patient-reported global disease activity" recorded with the PatGA PASDAS VAS. This resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Tender joint count

For the outcome "tender joint count", no statistically significant difference between the treatment groups was shown. This resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Swollen joint count

For the outcome "swollen joint count", no statistically significant difference between the treatment groups was shown. This resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Fatigue (FACIT-Fatigue)

For the outcome "fatigue" recorded with the FACIT-Fatigue, no statistically significant difference between the treatment groups was shown for the mean change. This resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

This corresponds to the assessment of the company, which additionally also considered the proportion of patients with an improvement of ≥ 4 points at week 52 and also did not derive an added benefit on the basis of this analysis.

Health-related quality of life

SF-36

MCS and PCS were considered separately for the outcome "health-related quality of life" recorded with the SF-36. In each case, there was no statistically significant difference between the treatment groups for the mean changes. In each case, this resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

For the MCS, this deviates from the assessment of the company, which derived an added benefit of secukinumab on the basis of the proportion of patients with an improvement of ≥ 5 points. For the PCS, this corresponds to the company's assessment.

DLQI

For the outcome "health-related quality of life" recorded with the DLQI, there was no statistically significant difference between the treatment groups for the proportion of patients with DLQI 0 or 1 at the end of the study. This resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

This deviates from the assessment of the company, which did not take into account the responder analyses for the derivation of the added benefit and derived an added benefit of secukinumab in comparison with adalimumab on the basis of the mean change of the DLQI.

Side effects

SAEs and discontinuation due to AEs

Operationalization

For the assessment of the outcomes "SAEs" and "discontinuation due to AEs", in addition to the overall rates, the company also presented analyses excluding events defined by the company as disease-specific AEs. These analyses were not used for the present benefit assessment because the events excluded by the company included AEs that cannot be attributed to the underlying disease. Overall, only 4 more events were included in the overall rates based on all events, so that the overall rates based on all events were taken into account for the present benefit assessment.

Results

Based on all events, there was no statistically significant difference between the treatment groups for each of the outcomes "SAEs" and "discontinuation due to AEs". In each case, this resulted in no hint of lesser or greater harm from secukinumab in comparison with adalimumab; lesser or greater harm is therefore not proven for any of these outcomes.

This concurs with the company's assessment.

Infections and infestations

No statistically significant difference between the treatment groups was shown for the outcome "infections and infestations". This resulted in no hint of lesser or greater harm from secukinumab in comparison with adalimumab; lesser or greater harm is therefore not proven.

This deviates from the assessment of the company, which saw a disadvantage for secukinumab on the basis of infections and infestations of mild severity.

2.3.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered in the present assessment:

- age (< 65 years/≥ 65 years)
- sex (female/male)

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there must be 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Subgroup analyses are available for all patient-relevant outcomes included (except for the outcomes "all-cause mortality" [no events occurred] and "infections and infestations" [not required, as there was no statistically significant result for the subpopulation]).

Table 14 shows the results of the subgroup analyses.

Table 14: Subgroups (morbidity) – RCT, direct comparison: secukinumab vs. adalimumab

Study Outcome	Secukinumab		Adalimumab		Secukinumab vs. adalimumab	
Characteristic Subgroup	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
EXCEED						
Skin symptoms (PASI 100)						
Age						
< 65 years	103	42.7[a] (41.5)	94	19.5[a] (20.8)	2.00 [1.26; 3.18][b]	0.003[b]
≥ 65 years[c]	7	1.1[a] (15.0)	7	5.0[a] (71.4)	–[d]	–[d]
Total					Interaction:	0.007[e]

a. Due to the multiple imputation of missing values, there is usually no whole number of patients with event.
b. Combining of RR, 95% CI and p-value across all imputation data sets using Rubin's rule.
c. 2 of 7 values (29%) were imputed by multiple imputation in the secukinumab arm; no values were imputed in the adalimumab arm.
d. No usable data; large difference between the treatment arms (29% vs. 0%) in the proportion of patients with imputed values. Information on the variables used for multiple imputation is missing. Thus, depending on the data constellation, there may also be a lesser benefit for secukinumab with regard to the PASI 100.
e. p-value refers to the effect measure OR. Since the RRs of the subgroups are not included in the respective other 95% CI, it can be assumed that the interaction p-value for the RR also provides a statistically significant result ($p < 0.05$). The interaction persists regardless of the imputation of values in the secukinumab arm.

CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; OR: odds ratio; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Skin symptoms (PASI 100)

An interaction by the characteristic "age" was shown for the outcome "skin symptoms" recorded with the PASI 100. For patients < 65 years of age, a statistically significant difference was shown in favour of secukinumab in comparison with adalimumab. Under consideration of the high risk of bias, this resulted in a hint of an added benefit of secukinumab in comparison with adalimumab. No usable data were available for patients ≥ 65 years of age. This was due to a large difference between the treatment arms (29% versus 0%) in the proportion of patients with imputed values, as well as missing information on the variables used for multiple imputation. Thus, depending on the data constellation, there may also be a lesser benefit for secukinumab with regard to the PASI 100. As a result, there was no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is not proven for this patient group.

2.3.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, 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 the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.3.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.3.2 (see Table 15).

Determination of the outcome category for symptom outcomes

The dossier does not provide information for every outcome considered in the present benefit assessment whether it was serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Skin symptoms recorded with the PASI 100

The allocation of skin symptoms (PASI 100) to a particular outcome category (serious or non-serious) depends on the patients' initial situation, and particularly on the severity and the grade of impairment from the symptoms measured with the PASI (psoriatic plaque redness, thickness and scaling).

The baseline data were used for assessing the severity of the symptoms. The mean PASI score at baseline for the patients in the subpopulation considered was below 20 (secukinumab arm: 16.2; adalimumab arm: 15.0). The mean PASI scores thus tended to be in a non-serious range [12,13]. The outcome "skin symptoms (PASI 100)" for these patients was therefore allocated to the category of non-serious/non-severe symptoms/late complications.

This deviates from the assessment of the company, which rated the patients' skin symptoms as serious.

Table 15: Extent of added benefit at outcome level: secukinumab vs. adalimumab (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Secukinumab vs. adalimumab** **Proportion of events (%) or mean change at end of study** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser benefit/added benefit not proven
Morbidity		
Minimal disease activity (MDA)	46.4% vs. 39.5% RR: 1.17 [0.85; 1.62] p = 0.325	Lesser benefit/added benefit not proven
Skin symptoms (PASI 100) Age < 65 years	41.50% vs. 20.76% RR: 2.00 [1.26; 3.18] p = 0.003 RR: 0.5 [0.31; 0.79][c] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
≥ 65 years	No usable data[d]	Lesser benefit/added benefit not proven
Physical functioning (HAQ-DI)	−0.60 vs. −0.56 MD: −0.05 [−0.19; 0.09] p = 0.517	Lesser benefit/added benefit not proven
Enthesitis (LEI)	−1.14 vs. −1.21 MD: 0.07 [−0.21; 0.35] p = 0.620	Lesser benefit/added benefit not proven
Dactylitis (LDI)	−19.72 vs. −18.88 MD: −0.85 [−2.34; 0.65] p = 0.267	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	20.31 vs. 22.57 MD: −2.26 [−7.95; 3.42] p = 0.433	Lesser benefit/added benefit not proven
Psoriatic arthritis-related pain (pain VAS)	−31.64 vs. −30.32 MD: −1.32 [−7.37; 4.73] p = 0.667	Lesser benefit/added benefit not proven
Patient-reported global disease activity (PatGA PASDAS VAS)	−38.70 vs. −38.14 MD: −0.56 [−7.16; 6.03] p = 0.866	Lesser benefit/added benefit not proven
Tender joint count	−14.92 vs. −14.48 MD: −0.44 [−1.94; 1.06] p = 0.564	Lesser benefit/added benefit not proven
Swollen joint count	−8.77 vs. −8.60 MD: −0.17 [−0.87; 0.52] p = 0.621	Lesser benefit/added benefit not proven
Fatigue (FACIT-Fatigue)	8.82 vs. 6.82 MD: 2.00 [−0.63; 4.62] p = 0.135	Lesser benefit/added benefit not proven

Table 15: Extent of added benefit at outcome level: secukinumab vs. adalimumab (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Secukinumab vs. adalimumab** **Proportion of events (%) or mean change at end of study** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
DLQI (0 or 1)	51.1% vs. 39.9% RR: 1.28 [0.94; 1.75] p = 0.118	Lesser benefit/added benefit not proven
SF-36		
Physical Component Summary	8.17 vs. 7.62 MD: 0.55 [−1.60; 2.70] p = 0.612	Lesser benefit/added benefit not proven
Mental Component Summary	7.62 vs. 5.32 MD: 2.30 [−0.41; 5.01] p = 0.096	Lesser benefit/added benefit not proven
Side effects		
SAEs	6.4% vs. 6.9% RR: 0.92 [0.33; 2.53] p = 0.869	Greater/lesser harm not proven
Discontinuation due to AEs	0.9% vs. 3.0% RR: 0.31 [0.03; 2.90] p = 0.302	Greater/lesser harm not proven
Infections and infestations (SOC, AE)	56.4% vs. 47.5% RR: 1.19 [0.91; 1.54] p = 0.203	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d. Large difference between the treatment arms (29% vs. 0%) in the proportion of patients with imputed values. Information on the variables used for multiple imputation is missing. Thus, depending on the data constellation, there may also be a lesser benefit for secukinumab with regard to the PASI 100.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ-DI: Health Assessment Questionnaire-Disability Index; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesitis Index; MD: mean difference; MDA: minimal disease activity; PASDAS: Psoriatic Arthritis Disease Activity Score; PASI: Psoriasis Area and Severity Index; PatGA: Patient Global Assessment of Disease Activity; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Table 16 summarizes the results 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 adalimumab

Positive effects	**Negative effects**
Non-serious/non-severe symptoms/late complications ▪ Skin symptoms (PASI 100) ▫ age (< 65 years): hint of added benefit – extent: “considerable”	–
PASI: Psoriasis Area and Severity Index	

In the overall consideration of the data, there is a positive effect of secukinumab in comparison with adalimumab. This effect is present for adult patients with active psoriatic arthritis aged < 65 years and with concomitant moderate to severe plaque psoriasis for the outcome “skin symptoms (PASI 100)”.

In the present situation, the added benefit of secukinumab is therefore based exclusively on an advantage in skin symptoms. However, there are no differences between secukinumab and adalimumab for the outcomes representing arthritis symptoms or for health-related quality of life. Overall, in this data situation, there is a hint of considerable added benefit of secukinumab in comparison with adalimumab for adult bDMARD-naive patients with active psoriatic arthritis aged < 65 years and with concomitant moderate to severe plaque psoriasis who have responded inadequately to previous DMARD therapy.

An added benefit of secukinumab in comparison with adalimumab is not proven for adult bDMARD-naive patients with active psoriatic arthritis aged ≥ 65 years and with concomitant moderate to severe plaque psoriasis who have responded inadequately to previous DMARD therapy.

No data are available for the administration of secukinumab in combination with methotrexate.

2.4 Research question 2: patients with active psoriatic arthritis who have responded inadequately to previous bDMARD therapy

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 list on secukinumab (status: 14 August 2020)
- bibliographical literature search on secukinumab (last search on 16 June 2020)
- search in trial registries for studies on secukinumab (last search on 17 June 2020)
- search on the G-BA website for secukinumab (last search on 17 June 2020)

To check the completeness of the study pool:

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

Concurring with the company, the check of the completeness of the study pool produced no RCTs on the direct comparison of secukinumab, alone or in combination with methotrexate, in comparison with the ACT.

2.4.2 Results on added benefit

In its dossier, the company presented no data for the assessment of the added benefit of secukinumab, alone or in combination with methotrexate, in comparison with the ACT for patients with active psoriatic arthritis who have responded inadequately to previous bDMARD therapy. This resulted in no hint of an added benefit of secukinumab in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

An added benefit is not proven because the company presented no data for the assessment of the added benefit of secukinumab, alone or in combination with methotrexate, in comparison with the ACT for patients with active psoriatic arthritis who have responded inadequately to previous bDMARD therapy.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of secukinumab, alone or in combination with methotrexate, in comparison with the ACT is summarized in Table 17.

Table 17: Secukinumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have responded inadequately to previous DMARD therapy[b, c]	A TNF-alpha antagonist **(adalimumab** or certolizumab pegol or etanercept or golimumab or infliximab) or an IL-17 inhibitor (ixekizumab), possibly in combination with methotrexate	Secukinumab alone in patients with concomitant moderate to severe plaque psoriasis: ▪ patients < 65 years: hint of a considerable added benefit[d] ▪ patients ≥ 65 years: added benefit not proven[e] Secukinumab in combination with methotrexate, or in patients without concomitant moderate to severe plaque psoriasis: ▪ Added benefit not proven
2	Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have responded inadequately to previous bDMARD therapy[b]	Switch to another biologic disease-modifying antirheumatic (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or ustekinumab), possibly in combination with methotrexate	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. According to the G-BA, the patient population considered for research questions 1 and 2 also includes patients who have not tolerated previous DMARD therapy.
c. The patient population considered for research question 1 consists of bDMARD-naive patients.
d. The added benefit results solely from an advantage in skin symptoms (PASI 100).
e. Depending on the data constellation, there may also be a lesser benefit of secukinumab.

ACT: appropriate comparator therapy; bDMARD: biologic DMARD; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; IL: interleukin; PASI: Psoriasis Area and Severity Index; TNF: tumour necrosis factor

For research question 1 (bDMARD-naive patients), the assessment described above deviates from that of the company, which derived an indication of considerable added benefit for secukinumab for all patients with concomitant moderate to severe plaque psoriasis regardless of age. Concurring with the present benefit assessment, the company did not claim an added benefit of secukinumab in patients without concomitant moderate to severe plaque psoriasis. The company did not consider the administration of secukinumab in combination with methotrexate separately.

For research question 2 (patients who have responded inadequately to previous bDMARD therapy), the assessment described above corresponds to that of the company, which claimed no added benefit.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. 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/a20-80.html.