IQWiG Reports – Commission No. A21-15

Upadacitinib (psoriatic arthritis) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Upadacitinib (Psoriasis-Arthritis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 April 2021). 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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Table of contents

List of tables[2]

Page

[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
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD	biologic disease-modifying antirheumatic drug
BSA	body surface area
csDMARD	conventional synthetic disease-modifying antirheumatic drug
DMARD	disease-modifying antirheumatic drug
EMA	European Medicines Agency
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
MTX	methotrexate
NRI	non-responder imputation
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PtGADA	Patient Global Assessment of Disease Activity
RCT	randomized controlled trial
SAE	serious adverse event
SAPS	Self-Assessment of Psoriasis Symptoms
SAPS-CT	SAPS-Clinical Trial
SAPS-RW	SAPS-Real World
SF-36	Short Form (36) Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SJC66	Swollen Joint Count 66

Abbreviation	Meaning
SOC	System Organ Class
SPARCC	Spondyloarthritis Research Consortium of Canada
SPC	Summary of Product Characteristics
TJC68	Tender Joint Count 68
TSS	total symptom score
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug upadacitinib. 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 1 February 2021.

Research question

The aim of the present report is the assessment of the added benefit of upadacitinib, alone or in combination with methotrexate (MTX), in comparison with the appropriate comparator therapy (ACT) in adult patients with active psoriatic arthritis who have had an inadequate response to a prior disease-modifying antirheumatic drug (DMARD) therapy.

The ACT specified by the G-BA differs depending on the pretreatment of the patients. The resulting research questions are shown in Table 2.

Table 2: Research questions of the benefit assessment of upadacitinib

Research question	Subindication	ACT[a]
1	Adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy[b]	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	Adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior therapy with biologic disease-modifying antirheumatic drugs (bDMARDs)	Switch to another biologic disease-modifying antirheumatic (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab 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. The patient population considered for research question 1 consists of bDMARD-naive patients.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; IL-17: interleukin-17; TNF: tumour necrosis factor

The company followed the specification of the ACT for both research questions. For research question 1, the company did not explicitly choose a drug from the named options, but included a study that compared upadacitinib with adalimumab. For research question 2, the company did not choose a drug from the named options and did not include any studies, either.

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

Research question 1: biologic disease-modifying antirheumatic drug (bDMARD)-naive patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior DMARD therapy

Study pool and study characteristics

The RCT SELECT-PsA 1 was included for the assessment of the added benefit. This study compared upadacitinib with adalimumab, each alone or in combination with MTX.

The study population includes adult patients with active moderate to severe psoriatic arthritis who had an inadequate response to at least 12 weeks of pretreatment with at least one conventional synthetic disease-modifying antirheumatic drug (csDMARD). Patients had to have ≥ 3 swollen and ≥ 3 tender joints, active plaque psoriasis (or documented history of plaque psoriasis), and a high-sensitivity C-reactive protein value above the upper limit of normal or ≥ 1 bone erosion on x-ray.

The company analysed results of a subpopulation that included only patients who received upadacitinib or adalimumab as monotherapy or together with MTX. This resulted in 355 patients in the upadacitinib arm and 352 patients in the adalimumab arm. All further information in the present assessment refers to this relevant subpopulation. Treatment with upadacitinib and adalimumab was in compliance with the Summaries of Product Characteristics (SPCs). In addition to MTX, concomitant treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and oral corticosteroids, among others, was also possible.

Risk of bias

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

The risk of bias was rated as low for the results of the following outcomes: Patient Global Assessment of Disease Activity (PtGADA), morning stiffness, pain, health status, and discontinuation due to adverse events (AEs). The risk of bias was rated as high for the results of the following outcomes: all-cause mortality, minimal disease activity (MDA), swollen and tender joint count, enthesitis, and all side effect outcomes except discontinuation due to AEs.

Results

All-cause mortality

No patients died in the SELECT-PsA 1 study. This resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven.

MDA

A statistically significant difference in favour of upadacitinib was shown for the outcome "MDA". Only one of the 3 conducted sensitivity analyses confirmed this effect regarding statistical significance using alternative imputation strategies (non-responder imputation [NRI] with variance correction). This resulted in a hint of an added benefit of upadacitinib in comparison with adalimumab.

Tender joints (TJC68 ≤ 1), swollen joints (SJC66 ≤ 1), enthesitis (SPARCC Enthesitis Index = 0), pain (pain NRS)

There was no statistically significant difference between the treatment groups for the following outcomes: Tender Joint Count 68 (TJC68), Swollen Joint Count 66 (SJC66), enthesitis (Spondyloarthritis Research Consortium of Canada [SPARCC] Enthesitis Index = 0), and pain (pain numeric rating scale [NRS]). In each case, this resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven.

Morning stiffness (severity and duration)

Data on severity and duration were recorded for the symptom "morning stiffness". A statistically significant difference in favour of upadacitinib was shown for both outcomes. The relevance of the results was checked in each case by means of Hedges' g. The 95% confidence intervals included the irrelevance threshold of −0.20 in each case. It can therefore not be inferred that the effect was relevant. In each case, this resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven.

PtGADA, health status (EQ-5D VAS)

A statistically significant difference in favour of upadacitinib was shown for each of the outcomes "PtGADA" and "health status" (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS]). The relevance of these results was checked by means of Hedges' g. The 95% confidence interval included the irrelevance threshold of −0.20 in each case. For either outcome, it can therefore not be inferred that the effect was relevant. In each case, this resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven.

Other morbidity outcomes

No usable data are available for each of the following outcomes: dactylitis, fatigue, ankylosing spondylitis, skin symptoms and physical functioning. In each case, this resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven.

Health-related quality of life

No usable data are available for outcomes on health-related quality of life. This resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven.

Overall rates of SAEs and discontinuations due to AEs

There was no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". In each case, this resulted in no hint of greater or lesser harm from upadacitinib in comparison with adalimumab; an added benefit is therefore not proven.

Infections and infestations (SOC, AE)

No statistically significant difference between the treatment groups was shown for the outcome "infections and infestations" (System Organ Class [SOC], AE). This resulted in no hint of greater or lesser harm from upadacitinib in comparison with adalimumab; an added benefit is therefore not proven.

Research question 2: patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior bDMARD therapy

No relevant study was identified for this research question. The company presented results of a placebo-controlled RCT (SELECT-PsA 2), but did not use them to derive an added benefit.

As the SELECT-PsA 2 study did not compare upadacitinib with the ACT, this study is not relevant for the assessment of the added benefit. Thus, no relevant data are available for research question 2 of the benefit assessment.

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

Based on the results presented, probability and extent of the added benefit of the drug upadacitinib in comparison with the ACT are assessed as follows:

Research question 1: bDMARD-naive patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior DMARD therapy

In the SELECT-PsA 1 study, a positive effect in favour of upadacitinib was only shown for the outcome "MDA".

In the company's dossier, no usable data were available for several patient-relevant outcomes in the therapeutic indication of psoriatic arthritis. This concerns outcomes on morbidity (dactylitis, axial involvement, skin symptoms, physical functioning), but especially also

[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].

outcomes on health-related quality of life. In contrast to the category of morbidity, no usable analyses are available here.

In summary, there is a hint of a minor added benefit of upadacitinib in comparison with adalimumab for adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior DMARD therapy.

Research question 2: patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior bDMARD therapy

The company did not present any data suitable for the derivation of an added benefit in patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior bDMARD therapy. An added benefit of upadacitinib in comparison with the ACT is therefore not proven.

Summary

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

Table 3: Upadacitinib – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy[b]	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	Hint of minor added benefit
Adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior therapy with biologic disease-modifying antirheumatic drugs (bDMARDs)	Switch to another biologic disease-modifying antirheumatic (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab 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. The patient population considered for research question 1 consists of bDMARD-naive patients.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; IL-17: interleukin-17; 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 upadacitinib, alone or in combination with MTX, in comparison with the ACT in adult patients with active psoriatic arthritis who have had an inadequate response to a prior DMARD therapy.

The ACT specified by the G-BA differs depending on the pretreatment of the patients. The resulting research questions are shown in Table 4.

Table 4: Research questions of the benefit assessment of upadacitinib

Research question	Subindication	ACT[a]
1	Adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy[b]	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	Adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior therapy with biologic disease-modifying antirheumatic drugs (bDMARDs)	Switch to another biologic disease-modifying antirheumatic (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab 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. The patient population considered for research question 1 consists of bDMARD-naive patients.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; IL-17: interleukin-17; 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 had an inadequate response or who have been intolerant to a prior DMARD therapy
- Research question 2: patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior bDMARD therapy

The company followed the specification of the ACT for both research questions. For research question 1, the company did not explicitly choose a drug from the named options, but included a study that compared upadacitinib with adalimumab. For research question 2, the company did not choose a drug from the named options and did not include any studies, either.

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 had an inadequate response or who have been intolerant to a prior 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 upadacitinib (status: 1 December 2020)
- bibliographical literature search on upadacitinib (last search on 1 December 2020)
- search in trial registries/trial results databases for studies on upadacitinib (last search on 1 December 2020)
- search on the G-BA website for upadacitinib (last search on 1 December 2020)

To check the completeness of the study pool:

- search in trial registries for studies on upadacitinib (last search on 3 February 2021)

The check did not identify any additional relevant studies.

2.3.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: upadacitinib 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 and other sources[c] yes/no [citation])
M15-572 (SELECT-PsA 1[d])	Yes	Yes	No	No	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. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to with this abbreviated form.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial; vs.: versus

The company also included the SELECT-PsA 1 study in its benefit assessment.

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: upadacitinib vs. adalimumab

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
SELECT-PsA 1	RCT, double-blind, parallel	Adults (≥ 18 years) with active psoriatic arthritis[b] and inadequate response to a non-biologic DMARD	Upadacitinib 15 mg (N = 430) upadacitinib 30 mg (N = 423)[c] adalimumab (N = 429) placebo 15 mg (N = 211)[c] placebo 30 mg (N = 212)[c] each as monotherapy or in combination with up to 1 or 2 DMARDs Relevant subpopulation thereof: upadacitinib 15 mg (n = 355) adalimumab (n = 352) each as monotherapy or in combination with MTX	Screening: 56 days Treatment: 56 weeks blinded (period 1), then another 3 years unblinded (period 2) Follow-up observation: in case of early treatment discontinuation 40 days (upadacitinib) or 70 days (adalimumab) for AEs[d] Data cut-offs: 13 December 2019: week 24 24 July 2020: week 56	281 centres in Argentina, Australia, Belarus, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Chile, China, Colombia, Croatia, Czech Republic, Estonia, Germany, Greece, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Malaysia, Mexico, Netherlands, New Zealand, Poland, Portugal, Puerto Rico, Russian Federation, Serbia, Singapore, Slovakia, Slovenia, South Africa, South Korea, Spain, Switzerland, Taiwan, Turkey, Ukraine, United Kingdom, United States 4/2017 – ongoing	Primary: response (ACR20) at week 12 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 ≥ 3 swollen and ≥ 3 tender joints, as well as hsCRP > ULN or ≥ 1 bone erosion, and active or documented history of plaque psoriasis.
c. The arm is not relevant for the assessment and is no longer presented in the following tables.
d. It is not clear from the information in Module 4 B whether all other outcomes were also followed up.

ACR20: 20% improvement in American College of Rheumatology criteria; AE: adverse event; CASPAR: Classification Criteria for Psoriatic Arthritis; DMARD: disease-modifying antirheumatic drug; hsCRP: high-sensitivity C-reactive protein; MTX: methotrexate; n: relevant subpopulation; N: number of randomized patients; RCT: randomised controlled trial; ULN: upper limit of normal; vs.: versus

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

Study	Intervention	Comparison
SELECT-PsA 1	Upadacitinib, 15 mg once daily, oral + placebo every 2 weeks, SC as monotherapy or in combination with MTX	Adalimumab, 40 mg, every 2 weeks, SC + placebo, once daily, oral as monotherapy or in combination with MTX
	Permitted pretreatment ▪ inadequate response to ≥ 1 non-biologic DMARD after ≥ 12 weeks of treatment **Non-permitted pretreatment** ▪ any biologic immunomodulators ▪ any JAK inhibitors (e.g. ruxolitinib, tofacitinib, filgotinib) **Permitted concomitant treatment** ▪ ≤ 2 non-biologic DMARDs (methotrexate, sulfasalazine, leflunomide, apremilast, hydroxychloroquine, bucillamine, iguratimod, or combination of methotrexate and leflunomide) for ≥ 12 weeks before baseline and ≥ 4 weeks at a stable dosage[a] ▪ NSAIDs, acetaminophen/paracetamol, weak opiates, oral or inhaled corticosteroids at a stable dosage ≥ 1 week before baseline ▪ tramadol or combination of acetaminophen and codeine or hydrocodone **Non-permitted concomitant treatment** ▪ opiates for ≥ 1 week before first study medication ▪ traditional Chinese medicine for ≥ 4 weeks before first study medication ▪ oral retinoids ≤ 4 weeks after baseline ▪ fumarates ≤ 1 week after baseline ▪ psoralen and UV-A ≤ 4 weeks after baseline ▪ UV-A or UV-B laser therapy ≤ 2 weeks after baseline ▪ all topical psoriasis treatments except mild emollients, weak corticosteroids or anti-itch treatments ▪ systemic strong CYP3A inhibitors or inducers ▪ live vaccines ≤ 4 weeks before baseline or live vaccination up to ≥ 4 weeks after last oral administration or ≥ 70 days after last subcutaneous administration of study medication	

a. Methotrexate: ≤ 25 mg/week, sulfasalazine: ≤ 3000 mg/week; leflunomide: ≤ 20 mg/day; apremilast: ≤ 60 mg/day; hydroxychloroquine: ≤ 40 mg/day; bucillamine: ≤ 300 mg/day; iguratimod: ≤ 50 mg/day.

CYP3A: cytochrome P450 3A; DMARD: disease-modifying antirheumatic drug; JAK: Janus kinase; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; SC: subcutaneous; vs.: versus

The RCT SELECT-PsA 1 study compared 2 dosages of upadacitinib (15 mg and 30 mg, each once daily), adalimumab and placebo. A total of 1705 patients were randomized in a 2:2:2:1:1 ratio to 2 upadacitinib arms, 1 adalimumab arm and 2 placebo arms. The arm with 30 mg upadacitinib and the 2 placebo arms are not relevant for the assessment and are not considered further.

The study population includes adult patients with active moderate to severe psoriatic arthritis who had an inadequate response to at least 12 weeks of pretreatment with at least one csDMARD. Patients had to have ≥ 3 swollen and ≥ 3 tender joints, active plaque psoriasis (or documented history of plaque psoriasis), and a high-sensitivity C-reactive protein value above the upper limit of normal or ≥ 1 bone erosion on x-ray.

Patients could receive up to 2 other non-biologic DMARDs concomitant to the study medication. However, upadacitinib is only approved as monotherapy or in combination with MTX [6]. The company therefore defined a subpopulation (referred to as "label population" in the dossier) that included only patients who received upadacitinib or adalimumab as monotherapy or together with MTX. This approach is appropriate. This resulted in 355 patients in the upadacitinib arm and 352 patients in the adalimumab arm. All further information in the present assessment refers to this relevant subpopulation.

Treatment with upadacitinib and adalimumab was in compliance with the SPCs [6,7]. In addition to MTX, concomitant treatment with NSAIDs and oral corticosteroids, among others, was also possible. Patients who did not show a response to therapy at week 16 of the treatment could have their concomitant therapy adjusted at this time. This means initiation or adjustment of MTX treatment, NSAIDs, analgesics or oral corticosteroids. Injection of corticosteroids into a peripheral joint, trigger point, tender point, bursa or enthesis was also possible. Additional information on therapy adjustments was not available in Module 4 A of the dossier. The company presented results of the most recent data cut-off, which was conducted after all patients had been treated for at least 56 weeks. The primary outcome of the study was the response according to American College of Rheumatology (ACR) criteria with at least 20% improvement at week 12 (ACR20).

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

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

Study Characteristic Category	Upadacitinib N[a] = 355	Adalimumab N[a] = 352
SELECT-PsA 1		
Age [years], mean (SD)	51 (12)	51 (12)
Sex [F/M], %	56/44	51/49
Tender joint count (TJC68), mean (SD)	20.4 (14.5)	19.9 (13.8)
Swollen joint count (SJC66), mean (SD)	11.8 (9.5)	11.6 (9.0)
Dactylitis (LDI > 0), n (%)	113 (31.8)	99 (28.1)
Enthesitis (LEI > 0), n (%)	221 (62.3)	215 (61.1)
Psoriatic spondylitis, n (%)	113 (31.8)	102 (29.0)
Morning stiffness total 0-10, mean (SD)	5.6 (2.6)	5.2 (2.6)
PASI, mean (SD)	10.3 (10.3)[b]	9.9 (8.9)[b]
Pain (pain NRS), mean (SD)	6.2 (2.1)	6.0 (2.1)
Physical functioning (HAQ-DI), mean (SD)	1.2 (0.6)	1.1 (0.6)
Patient assessment of disease activity (PtGADA), mean (SD)	6.6 (2.0)	6.4 (2.0)
Time since PsA diagnosis [years], median [Q1; Q3]	3.4 [1.1; 7.8]	3.4 [1.1; 7.4]
Family origin, n (%)		
White	325 (91.5)	313 (88.9)
Black or African American	1 (0.3)	2 (0.6)
Indian/Native Alaskan	0	2 (0.6)
Hawaiian/Pacific	0	1 (0.3)
Asian	24 (6.8)	29 (8.2)
Various	5 (1.4)	5 (1.4)
Geographical region, n (%)		
North America	61 (17.2)	63 (17.9)
Western Europe or Oceania	44 (12.4)	34 (9.7)
Eastern Europe	178 (50.1)	162 (46.0)
Latin America	39 (11.0)	52 (14.8)
Asia	20 (5.6)	26 (7.4)
Other	13 (3.7)	15 (4.3)
Number of prior csDMARD therapies, n (%)		
0	1 (0.3)	2 (0.6)
1	260 (73.2)	265 (75.3)
2	68 (19.2)	69 (19.6)
≥ 3	26 (7.3)	16 (4.5)
Current csDMARD therapy, n (%)		
Yes	279 (78.6)	269 (76.4)
No	76 (21.4)	83 (23.6)

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

Study Characteristic Category	Upadacitinib N[a] = 355	Adalimumab N[a] = 352
NSAID at baseline, n (%)		
Yes	214 (60.3)	224 (63.6)
No	141 (39.7)	128 (36.4)
Corticosteroids at baseline, n (%)		
Yes	59 (16.6)	61 (17.3)
No	296 (83.4)	291 (82.7)
Adjustment of background therapy at week 16, n (%)	27 (7.6)	36 (10.2)
Treatment discontinuation until week 56 n (%)	50 (14.1)	61 (17.3)
Study discontinuation until week 56, n (%)	37 (10.4)	47 (13.4)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Based on patients with a BSA > 3%; 183 (51.5%) in the intervention arm and 181 (51.4%) in the control arm.

BSA: body surface area; csDMARD: conventional synthetic disease-modifying antirheumatic drug; F: female; HAQ-DI: Health Assessment Questionnaire-Disability Index; M: male; n: number of patients in the category; N: number of randomized patients; NRS: numeric rating scale; NSAID: nonsteroidal anti-inflammatory drug; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis; PtGADA: Patient Global Assessment of Disease Activity; RCT: randomized controlled trial; SD: standard deviation; SJC: swollen joint count; TJC: tender joint count; vs.: versus

There were no major differences between the arms of the SELECT-PsA 1 study.

The mean age of the patients was 51 years, and the sex ratio was almost balanced. About 90% were white, with almost 50% of the patients coming from Eastern Europe, otherwise mainly from North America (about 18%), Western Europe/Oceania (about 11%) and Latin America (about 13%).

The patients had an average of 20 tender and 12 swollen joints. Dactylitis was present in 30%, enthesitis in just over 60% and spondylitis in 30%. If patients had morning stiffness, this was moderate on average. The median time since diagnosis of psoriatic arthritis was 3.4 years.

With few exceptions, all patients were pretreated with at least one csDMARD, of which about 3 quarters were treated with exactly one drug. About the same number of patients were receiving continued treatment with a csDMARD at baseline, according to the definition of the relevant subpopulation with MTX. Concomitant treatment with NSAIDs at baseline was given to slightly more than 60% of the participants. In contrast, fewer than 20% received therapy with corticosteroids. An adjustment of the antirheumatic background therapy due to non-response to the study medication at week 16 was made in 7.6% of the patients in the upadacitinib arm and in 10.2% in the adalimumab arm.

About 16% of the patients discontinued the study medication prematurely, and about 12% participation in the study.

Transferability to the German health care context

The company stated that the SELECT-PsA 1 study was conducted worldwide and that 90.2% of the study population were white participants. Due to the structural equality of the study population and the approval population, the company assumed that the effects observed in the study also occurred under everyday conditions and were transferable to the German health care context. Effect modifications due to the factor of region did not occur in the study. There were no indications that would contradict a transferability. In addition, the European Medicines Agency (EMA) had confirmed the external validity of the approval studies with regard to the comparability of European and non-European patients. The company did not provide any further information on the transferability to the German health care context.

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: upadacitinib 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			
SELECT-PsA 1	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 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

- swollen joint count, recorded with the SJC66
- tender joint count, recorded with the TJC68
- enthesitis, recorded with the SPARCC Enthesitis Index
- dactylitis, recorded with the Leeds Dactylitis Index (LDI)
- skin symptoms, recorded with the Psoriasis Area and Severity Index (PASI)
- skin symptoms, recorded with the Self-Assessment of Psoriasis Symptoms (SAPS)
- axial involvement, recorded with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- physical functioning, recorded with the Health Assessment Questionnaire-Disability Index (HAQ-DI)
- morning stiffness (severity and duration)
- pain, recorded with the pain NRS
- fatigue, recorded with the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue
- PtGADA
- health status, recorded with the EQ-5D VAS

- Health-related quality of life
  - Short Form 36 Health Survey (SF-36)
- Side effects
  - AEs, presented as supplementary information
  - serious AEs (SAEs)
  - discontinuation due to AEs
  - infections and infestations (SOC, AE)
  - 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 A).

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

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

Study	Outcomes																		
	All-cause mortality	MDA	Swollen joint count (SJC66)	Tender joint count (TJC68)	Enthesitis (SPARCC Enthesitis Index)	Dactylitis (LDI)	Skin symptoms (PASI, SAPS)	Axial involvement (BASDAI)	Physical functioning (HAQ-DI)	Morning stiffness (severity and duration)	Pain (pain NRS)	Fatigue (FACIT-Fatigue)	PtGADA	Health status (EQ-5D VAS)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Infections and infestations (SOC, AE)	Further specific AEs
SELECT-PsA 1	Yes	Yes	Yes	Yes	Yes	No[a]	No[a]	No[a]	No[a]	Yes	Yes	No[a]	Yes	Yes	No[a]	Yes	Yes	Yes	No[b]

a. No usable data available; see Section 2.3.2.1 for reasons.
b. No further specific AEs were identified.

AE: adverse event; BASDAI: Bath Ankylosing Spondylitis Disease Activity 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; MDA: minimal disease activity; NRS: numeric rating scale; PASI: Psoriasis Area and Severity Index; PtGADA: Patient Global Assessment of Disease Activity; RCT: randomized controlled trial; SAE: serious adverse event; SAPS: Self-Assessment of Psoriasis Symptoms; SF-36: Short Form 36; SJC: swollen joint count; SOC: System Organ Class; SPARCC: Spondyloarthritis Research Consortium of Canada; TJC: tender joint count; VAS: visual analogue scale; vs.: versus

The company's dossier did not contain usable data for all outcomes listed in Table 10. In addition, the company included further outcomes that were not used for this benefit assessment. This is explained below.

Analyses based on a limited study population

For the following outcomes, the company included only patients with baseline disease activity in relation to the instrument used:

- SPARCC Enthesitis Index: only patients with SPARCC > 0 at baseline
- LDI: only patients with LDI > 0 at baseline
- PASI: only patients with psoriasis on ≥ 3% of the body surface area (BSA) at baseline
- BASDAI: only patients with spondylitis at baseline

The approach of the company is not appropriate. Patients who, for example, do not have enthesitis or only minor skin symptoms at baseline are, in principle, also at risk of developing these symptoms in the further course of the disease. Thus, the total study population and the relevant subpopulation are at risk for these outcomes. Due to the operationalization chosen by the company, it may not be possible to derive conclusions for the total target population. It is therefore necessary to include the relevant subpopulation in the analysis of these outcomes. Under certain circumstances, however, an analysis based on a limited population can still be suitable for drawing a conclusion for the total target population if its proportion of the target population is large enough. In the present assessment, this applies to the outcome "SPARCC Enthesitis Index", as > 70% of the relevant subpopulation was included in the analysis here. With 70% of the relevant subpopulation missing in the analysis for the outcome "LDI", 48.5% for the outcome "PASI" and 69.6% for the outcome "BASDAI", this is not the case for the other outcomes mentioned. The analyses on these outcomes are therefore not usable.

In Module 4 A, the company presented analyses for the outcome "Leeds Enthesitis Index (LEI)" used in previous assessments [8,9]. For this outcome also, only analyses based on a limited study population are available (38% of the relevant subpopulation were missing in the analyses) and are therefore not usable.

The instruments TJC68, SJC66, PASI, PtGADA, HAQ-DI and LEI were also the basis for recording the MDA. For classification as an MDA responder, 5 of the following 7 criteria must be met: SJC68 ≤ 1; TJC66 ≤ 1; PASI score ≤ 1 or BSA ≤ 3%; patient assessment of pain ≤ 1.5; PtGADA ≤ 2; HAQ-DI ≤ 0.5; LEI ≤ 1. It is assumed that in this case the complete population was used in the analysis, as the company did not provide any information in Module 4 A that only a limited patient population was included for the outcome "MDA".

Outcomes with unsuitable response criteria

The company conducted responder analyses for a number of patient-reported outcomes. However, the response criteria applied are not suitable for the assessment of the added benefit. This affects the following outcomes:

- HAQ-DI: proportion of patients with an improvement in HAQ-DI of ≥ 0.35 points at week 56 (on a scale of 0 to 3 points)
- FACIT-Fatigue: proportion of patients with an improvement in the FACIT-Fatigue total score of ≥ 4 points at week 56 (on a scale of 0 to 52 points)
- SF-36: proportion of patients with an improvement of the SF-36 Physical Component Summary (PCS) or Mental Component Summary (MCS) of ≥ 5 points each at week 56 (normalized scale with a minimum of approximately 7 [PCS] or 6 [MCS] and a maximum of approximately 70 each; for explanation see [10])

The analyses conducted by the company were not used for the dossier assessment. As explained in the *General Methods* of the Institute [1], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range), which was not the case in the response criteria mentioned.

The responder analyses presented by the company for the HAQ-DI are provided as supplementary information in Appendix B of the full dossier assessment.

Unvalidated analyses on patient-reported outcome

- SAPS

The SAPS is a measurement instrument for the assessment of psoriasis with 2 validated versions: SAPS-Clinical Trial (SAPS-CT) and SAPS-Real World (SAPS-RW).

The SAPS-CT contains 9 items that record the symptoms of the last 24 hours, asking the patients to indicate the most severe symptoms in each case. The SAPS-RW contains 6 items that refer to the last 7 days and ask for the average severity of symptoms. The items are answered on NRS from 0 (no symptoms) to 10 (severe symptoms). The total symptom score (TSS) is calculated by adding the item scores and calculating the mean value, excluding the item on joint pain. This results in a scale range of 0 to 10 for both instruments. The item on joint pain is analysed separately. Higher scores indicate more severe symptoms [11].

The SELECT-PsA 1 study presented by the company used a preliminary version of the SAPS with 11 items. The recording was based on a 24-hour recall period, but it was not stated whether the worst symptoms or the average severity of symptoms were rated. In Module 4 A, the company presented a sum score of all 11 items. The sources provided by the company do not indicate that this preliminary version of the SAPS has been validated. Furthermore, no analysis

algorithm is described for the preliminary version. Therefore, the analysis of the SAPS presented by the company cannot be used.

However, it can be inferred from the validation publication [11] that the items from the preliminary version were not modified for the final instruments SAPS-CT and SAPS-RW. An analysis of the SAPS-CT or SAPS-RW taking into account the recall period as described in the validation publication is required.

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: upadacitinib vs. adalimumab

Study	Outcomes																			
	Study level	All-cause mortality	MDA	Swollen joint count (SJC66)	Tender joint count (TJC68)	Enthesitis (SPARCC Enthesitis Index)	Dactylitis (LDI)	Skin symptoms (PASI)	Axial involvement (BASDAI)	Physical functioning (HAQ-DI)	Morning stiffness (severity and duration)	Pain (pain NRS)	Fatigue (FACIT-Fatigue)	PtGADA	Health status (EQ-5D VAS)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Infections and infestations (SOC, AE)	Further specific AEs
SELECT-PsA 1	L	H[a]	H[b]	H[b]	H[b]	H[b, d]	–[c]	–[c]	–[c]	–[c]	L	L	–[c]	L	L	–[c]	H[a]	L	H[a]	–[e]

a. Potential differences in follow-up observation periods between the treatment arms (upadacitinib arm: 30 days; adalimumab arm: 70 days).
b. Large proportion of patients who were rated as non-responders due to missing values (> 10% in each of both treatment arms).
c. No usable data available; for reasons, see Section 2.3.2.1.
d. Large proportion of patients (> 10%) not considered in the analysis.
e. No further specific AEs were identified.

AE: adverse event; BASDAI: Bath Ankylosing Spondylitis Disease Activity 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; MDA: minimal disease activity; NRS: numeric rating scale; PASI: Psoriasis Area and Severity Index; PtGADA: Patient Global Assessment of Disease Activity; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form 36; SJC: swollen joint count; SOC: System Organ Class; SPARCC: Spondyloarthritis Research Consortium of Canada; TJC: tender joint count; VAS: visual analogue scale; vs.: versus

The risk of bias of the results in the SELECT-PsA 1 study varies by outcome. The risk of bias of the results was rated as low for the following outcomes: PtGADA, morning stiffness, pain, health status (EQ-5D), and discontinuation due to AEs. This deviates from the assessment of the company, which assumed a low risk of bias in each case.

The risk of bias was rated as high for the results of the following outcomes: all-cause mortality (recorded using the AE analysis), MDA, swollen joint count (SJC66) and tender joint count (TJC68), enthesitis (SPARCC), and side effect outcomes (except discontinuation due to AEs). For all AEs, among which all-cause mortality was also recorded, there were potential differences in the observation periods between the treatment arms, namely 30 days in the upadacitinib arm and 70 days in the adalimumab arm. For the results of the other outcomes mentioned, the high risk of bias was due to a high proportion of patients who were rated as non-responders due to missing values, and for the SPARCC Enthesitis Index also due to a high proportion of patients (> 10%) who were not considered at all in the analysis.

For the outcomes "MDA", "swollen joint count" (SJC66) and "tender joint count" (TJC68), this is in line with the assessment of the company. For the outcomes in the categories of mortality and side effects, this differs from the assessment of the company, which assumed a low risk of bias for the results of these outcomes. The company presented the results of the SPARCC Enthesitis Index only as supplementary information without assessing the risk of bias.

For outcomes with a high risk of bias of the results and a statistically significant result, the company performed sensitivity analyses using multiple imputation to check the robustness of the results. In the SELECT-PsA 1 study, this concerns the outcome "MDA". Based on this, the company considered the results of this outcome to be sufficiently informative to derive an indication. In the case of statistically significant results, alternative sensitivity analyses (Institute's calculations using imputation strategies according to Higgins 2008 [12]) were carried out for the present benefit assessment besides the primary analysis, in which patients with missing values or after discontinuation of the study medication were imputed as non-responders, in order to check the robustness of the estimated effects.

2.3.2.3 Results

Table 12 and Table 13 summarize the results of the comparison of upadacitinib with adalimumab in bDMARD-naive patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior DMARD therapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Results on common AEs are presented in Appendix A of the full dossier assessment.

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

Study Outcome category Outcome	Upadacitinib		Adalimumab		Upadacitinib vs. adalimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
SELECT-PsA 1					
Mortality					
All-cause mortality	355	0 (0)	352	0 (0)	–
Morbidity					
MDA[b, c]	355	173 (48.7)	352	141 (40.1)	1.22 [1.03; 1.44]; 0.021
Sensitivity analyses:					
ACA[d]	299	173 (57.9)	283	141 (49.8)	1.16 [1.00; 1.35]; 0.053[e]
NRI[c] with variance correction	355	173 (48.7)	352	141 (40.1)	1.22 [1.01; 1.46]; 0.037[e, f]
ICA-pc[g] with variance correction	355	201 (56.6)	352	175 (49.8)	1.14 [0.97; 1.32]; 0.104[e, f]
Tender joints (TJC68 ≤ 1)[c]	355	164 (46.2)	352	143 (40.6)	1.14 [0.96; 1.34]; 0.139
Swollen joints (SJC66 ≤ 1)[c]	355	236 (66.5)	352	208 (59.1)	1.12 [1.00; 1.25]; 0.052
Enthesitis (SPARCC Enthesitis Index = 0)[c]	268	158 (59.0)	261	143 (54.8)	1.07 [0.93; 1.24]; 0.350
Dactylitis (LDI = 0)	No suitable data available				
Fatigue (FACIT-Fatigue)	No suitable data available				
Axial involvement (BASDAI)	No suitable data available				
Skin symptoms (PASI)	No suitable data available				
Physical functioning (HAQ-DI)	No suitable data available				
Health-related quality of life					
SF-36	No suitable data available				
Side effects					
AEs (supplementary information)	355	272 (76.6)	352	272 (77.3)	–
SAEs	355	23 (6.5)	352	28 (8.0)	0.81 [0.48; 1.39]; 0.449
Discontinuation due to AEs	355	16 (4.5)	352	23 (6.5)	0.69 [0.37; 1.28]; 0.241
Infections and infestations (SOC, AE)	355	192 (54.1)	352	167 (47.4)	1.14 [0.99; 1.32]; 0.078

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

Study Outcome category Outcome	Upadacitinib N	Upadacitinib Patients with event n (%)	Adalimumab N	Adalimumab Patients with event n (%)	Upadacitinib vs. adalimumab RR [95% CI]; p-value[a]

a. RR, 95% CI and p-value from a generalized linear model adjusted for DMARD treatment at baseline (yes, no) or without adjustment (side effect outcomes).
b. For classification as an MDA responder, 5 of the following 7 criteria must be met: TJC68 ≤ 1; SJC66 ≤ 1; PASI score ≤ 1 or BSA ≤ 3%; patient assessment of pain ≤ 1.5; PtGADA ≤ 2, HAQ-DI ≤ 0.5, and LEI ≤ 1.
c. Missing values imputed using NRI.
d. Analysis is exclusively based on patients with complete observation.
e. Institute's calculation, asymptotic.
f. Institute's calculation, estimation of variance according to the dataset re-sizing approach (approach W3 in [12]).
g. In both treatment groups, the missing values are imputed according to the observed risk in the control group.

ACA: available case analysis; AE: adverse event; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BSA: body surface area; CI: confidence interval; DMARD: disease-modifying antirheumatic drug; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ-DI: Health Assessment Questionnaire-Disability Index; ICA-pc: imputed case analysis according to control group risk; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesitis Index; MDA: minimal disease activity; N: number of analysed patients; n: number of patients with (at least one) event; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36: Short Form 36; SJC: swollen joint count – 66 joints; SOC: System Organ Class; SPARCC: Spondyloarthritis Research Consortium of Canada; TJC68: tender joint count – 68 joints; vs.: versus

Table 13: Results (morbidity, continuous) – RCT, direct comparison: upadacitinib vs. adalimumab

Study Outcome category Outcome	Upadacitinib			Adalimumab			Upadacitinib vs. adalimumab
	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)[b]	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)[b]	MD [95% CI]; p-value[b]
SELECT-PsA 1							
Morbidity							
Morning stiffness[c]							
Severity[d]	341	6.19 (2.66)	−3.33 (0.12)	348	5.81 (2.78)	−2.79 (0.12)	−0.54 [−0.84; −0.23]; < 0.001 Hedges' g: −0.24 [−0.39; −0.09]
Duration[e]	341	5.03 (3.05)	−2.59 (0.11)	348	4.62 (3.00)	−2.21 (0.11)	−0.38 [−0.66; −0.11]; 0.006 Hedges' g: −0.19 [−0.34; −0.04]
Pain (pain NRS)[c]	347	6.20 (2.05)	−2.76 (0.10)	350	6.00 (2.11)	−2.52 (0.10)	−0.23 [−0.49; 0.03]; 0.079
Global disease activity (PtGADA)[c]	347	6.61 (2.03)	−3.10 (0.10)	350	6.39 (2.01)	−2.85 (0.10)	−0.26 [−0.51; −0.004]; 0.047 Hedges' g: −0.14 [−0.29; 0.01]
Health status (EQ-5D VAS)[f]	341	53.53 (21.67)	17.99 (0.98)	348	53.62 (21.15)	15.48 (0.95)	2.51 [0.08; 4.93]; 0.043 Hedges' g: 0.14 [−0.01; 0.29]

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. Mean and SE (change per treatment arm) and MD, 95% CI and p-value (group comparison): MMRM analysis with the variables treatment, visit, DMARD treatment at baseline, value at baseline, and the interaction term treatment and visit.
c. Recorded on a scale from 0 to 10; lower (decreasing) values indicate lower disease activity or symptoms; negative effects (intervention minus control) indicate an advantage for the intervention.
d. Recorded using the BASDAI item 5.
e. Recorded using the BASDAI item 6.
f. Higher (increasing) values indicate better health status; positive effects (intervention minus control) indicate an advantage for the intervention.

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CI: confidence interval; DMARD: disease-modifying antirheumatic drug; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference, MMRM: mixed-effects model with repeated measures; N: number of analysed patients; NRS: numeric rating scale; PtGADA: Patient Global Assessment of Disease Activity; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Based on the available data, at most indications, e.g. of an added benefit, can be determined for the following outcomes: morning stiffness, pain, patient assessment of disease activity, health status, and discontinuation due to AEs; at most hints can be determined for the following outcomes: all-cause mortality, MDA, swollen and tender joints, enthesitis, as well as for side effect outcomes (except discontinuation due to AEs).

Mortality

All-cause mortality

No patients died in the SELECT-PsA 1 study. This resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven. This concurs with the company's assessment.

Morbidity

MDA

A statistically significant difference in favour of upadacitinib was shown for the outcome "MDA". Only one of the 3 conducted sensitivity analyses confirmed this effect regarding statistical significance using alternative imputation strategies (NRI with variance correction) (see Table 12). This resulted in a hint of an added benefit of upadacitinib in comparison with adalimumab.

This deviates from the assessment of the company, which derived an indication of an added benefit.

Tender joints (TJC68 ≤ 1)

No statistically significant difference between the treatment groups was shown for the outcome "TJC68". This resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven. This concurs with the company's assessment.

Swollen joints (SJC66 ≤ 1)

No statistically significant difference between the treatment groups was shown for the outcome "SJC66". This resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven. This concurs with the company's assessment.

Enthesitis (SPARCC Enthesitis Index = 0)

No statistically significant difference between the treatment groups was shown for the outcome "enthesitis". This resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven. This deviates from the assessment of the company, which derived a hint of an added benefit for enthesitis on the basis of the results on the LEI.

Morning stiffness (severity and duration)

Data on severity and duration were recorded for the symptom "morning stiffness". A statistically significant difference in favour of upadacitinib was shown for both outcomes. The relevance of the results was checked in each case by means of Hedges' g. The 95% confidence intervals included the irrelevance threshold of −0.20 in each case. It can therefore not be inferred that the effect was relevant. In each case, this resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an indication of an added benefit for each of these 2 outcomes.

Pain (pain NRS)

No statistically significant difference between the treatment groups was shown for the outcome "pain". This resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven. This concurs with the company's assessment.

PtGADA

A statistically significant difference in favour of upadacitinib was shown for the outcome "PtGADA". The relevance of this result was checked by means of Hedges' g. The 95% confidence interval includes the irrelevance threshold of −0.20. It can therefore not be inferred that the effect was relevant. This resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven.

This deviates from the company's assessment, which derived a hint of an added benefit.

Health status (EQ-5D VAS)

A statistically significant difference in favour of upadacitinib was shown for the outcome "health status". The relevance of this result was checked by means of Hedges' g. The 95% confidence interval includes the irrelevance threshold of −0.20. It can therefore not be inferred that the effect was relevant. This resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven.

This deviates from the company's assessment, which derived a hint of an added benefit.

Other morbidity outcomes

No usable data are available for each of the following outcomes: dactylitis, fatigue, axial involvement, skin symptoms and physical functioning. In each case, this resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven.

For the outcomes "dactylitis" (LDI), "skin symptoms" (PASI) and "fatigue" (FACIT-Fatigue), this is consistent with the assessment of the company.

The company derived an indication of an added benefit for each of the outcomes "axial involvement" (BASDAI) and "physical functioning" (HAQ-DI).

Health-related quality of life

No usable data are available for outcomes on health-related quality of life. This resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an indication of an added benefit on the basis of the SF-36.

Side effects

Overall rates of SAEs and discontinuations due to AEs

There was no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". In each case, this resulted in no hint of greater or lesser harm from upadacitinib in comparison with adalimumab; an added benefit is therefore not proven. This concurs with the company's assessment.

Infections and infestations (SOC, AE)

No statistically significant difference between the treatment groups was shown for the outcome "infections and infestations" (SOC, AE). This resulted in no hint of greater or lesser harm from upadacitinib in comparison with adalimumab; an added benefit is therefore not proven. This concurs with the company's assessment.

2.3.2.4 Subgroups and other effect modifiers

The subgroup characteristics of age, sex and disease severity were to be considered for the present dossier assessment. However, in the dossier, the company did not examine suitable characteristics that could be used to characterize the severity of the disease.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to 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.

There was no statistically significant interaction for any of the included outcomes. Subgroup results are therefore not presented.

2.3.3 Probability and extent of added benefit

Probability and extent of the added benefit are derived below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on 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 14).

Determination of the outcome category for symptom outcomes

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they are serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Outcome "minimal disease activity"

There was a hint of an added benefit for the outcome "MDA". The MDA is defined as meeting at least 5 of the following 7 criteria: TJC68 ≤ 1; SJC66 ≤ 1; PASI ≤ 1 or psoriasis BSA ≤ 3%; patient assessment of pain ≤ 1.5; PtGADA ≤ 2; HAQ-DI ≤ 0.5; LEI ≤ 1.

The company's dossier did not contain summarizing information on the severity of psoriatic arthritis at baseline. However, an examination of TJC68, SJC66, pain, HAQ-DI and PtGADA showed a high number of affected joints and high patient-reported pain score and disease activity with values in the upper scale ranges (see Table 8). Therefore, the patients' symptoms was rated as serious/severe and the achievement of an MDA was assigned to this category accordingly.

Table 14: Extent of added benefit at outcome level: upadacitinib vs. adalimumab (multipage table)

Outcome category **Outcome**	**Upadacitinib vs. adalimumab** **Proportion of events (%) or mean change in the course of the 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		
MDA	48.7% vs. 40.1% RR: 1.22 [1.03; 1.44] RR: 0.82 [0.70; 0.97][c]; p = 0.021 probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Tender joints (TJC68 < 1)	46.2% vs. 40.6% RR: 1.14 [0.96; 1.34]; p = 0.139	Lesser benefit/added benefit not proven
Swollen joints (SJC66 < 1)	66.5% vs. 59.1% RR: 1.12 [1.00; 1.25]; p = 0.052	Lesser benefit/added benefit not proven
Enthesitis (SPARCC Enthesitis Index = 0)	59.0% vs. 54.8% RR: 1.07 [0.93; 1.24]; p = 0.350	Lesser benefit/added benefit not proven
Morning stiffness (severity)	−3.33 vs. −2.79 MD: −0.54 [−0.84; −0.23]; p < 0.001 Hedges' g: −0.24 [−0.39; −0.09][d]	Lesser benefit/added benefit not proven
Morning stiffness (duration)	−2.59 vs. −2.21 MD: −0.38 [−0.66; −0.11]; p = 0.006 Hedges' g: −0.19 [−0.34; −0.04][d]	Lesser benefit/added benefit not proven
Pain (pain NRS)	−2.76 vs. −2.52 MD: −0.23 [−0.49; 0.03]; p = 0.079	Lesser benefit/added benefit not proven
Global disease activity (PtGADA)	−3.10 vs. −2.85 MD: −0.26 [−0.51; −0.004]; p = 0.047 Hedges' g: −0.14 [−0.29; 0.01][d]	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	17.99 vs. 15.48 MD: 2.51 [0.08; 4.93]; p = 0.043 Hedges' g: 0.14 [−0.01; 0.29][d]	Lesser benefit/added benefit not proven
Dactylitis (LDI = 0)	No suitable data available	Lesser benefit/added benefit not proven

Table 14: Extent of added benefit at outcome level: upadacitinib vs. adalimumab (multipage table)

Outcome category **Outcome**	**Upadacitinib vs. adalimumab** **Proportion of events (%) or mean change in the course of the study** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Fatigue (FACIT-Fatigue)	No suitable data available	Lesser benefit/added benefit not proven
Axial involvement (BASDAI)	No suitable data available	Lesser benefit/added benefit not proven
Skin symptoms (PASI)	No suitable data available	Lesser benefit/added benefit not proven
Physical functioning (HAQ-DI)	No suitable data available	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36	No suitable data available	Lesser benefit/added benefit not proven
Side effects		
SAEs	6.5% vs. 8.0% RR: 0.81 [0.48; 1.39]; p = 0.449	Greater/lesser harm not proven
Discontinuation due to AEs	4.5% vs. 6.5% RR: 0.69 [0.37; 1.28]; p = 0.241	Greater/lesser harm not proven
Infections and infestations (AEs)	54.1% vs. 47.4% RR: 1.14 [0.99; 1.32]; p = 0.078	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. If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a clinically relevant effect. In other cases, the presence of a clinically relevant effect cannot be inferred.

AE: adverse event; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CI: confidence interval; CI_u: upper limit of confidence interval; 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; NRS: numeric rating scale; PASI: Psoriasis Area and Severity Index; PtGADA: Patient Global Assessment of Disease Activity; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36: Short Form 36; SJC66: swollen joint count – 66 joints; SPARCC: Spondyloarthritis Research Consortium of Canada; TJC68: tender joint count – 68 joints; VAS: visual analogue scale; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Table 15 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of upadacitinib in comparison with adalimumab

Positive effects	Negative effects
Hint of an added benefit – extent "minor" (serious/severe symptoms/late complications: MDA)	-
MDA: minimal disease activity	

In the SELECT-PsA 1 study, a positive effect in favour of upadacitinib was only shown for the outcome "MDA".

In the company's dossier, no usable data were available for several patient-relevant outcomes in the therapeutic indication of psoriatic arthritis. This concerns outcomes on morbidity (dactylitis, axial involvement, skin symptoms, physical functioning), but especially also outcomes on health-related quality of life. In contrast to the category of morbidity, no usable analyses are available here.

In summary, there is a hint of a minor added benefit of upadacitinib in comparison with adalimumab for adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior DMARD therapy.

2.4 Research question 2: patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior 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 upadacitinib (status: 1 December 2020)
- bibliographical literature search on upadacitinib (last search on 1 December 2020)
- search in trial registries/trial results databases for studies on upadacitinib (last search on 1 December 2020)
- search on the G-BA website for upadacitinib (last search on 1 December 2020)

To check the completeness of the study pool:

- search in trial registries for studies on upadacitinib (last search on 3 February 2021)

No relevant study was identified from the check.

The company also stated that it had not identified any relevant study for this research question. However, it presented results of a placebo-controlled RCT (SELECT-PsA 2), but did not use them to derive an added benefit.

The SELECT-PsA 2 study included adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior bDMARD therapy [13]. Patients were randomized in a 2:2:1:1 ratio to upadacitinib 15 mg once daily, upadacitinib 30 mg once daily, or one of 2 placebo arms. In the placebo arms, treatment was switched to upadacitinib 15 mg or upadacitinib 30 mg after 24 weeks.

As the SELECT-PsA 2 study did not compare upadacitinib with the ACT, this study is not relevant for the assessment of the added benefit. Thus, no relevant data are available for research question 2 of the benefit assessment.

2.4.2 Results on added benefit

The company did not submit any relevant studies comparing upadacitinib with the ACT. Thus, there is no hint of an added benefit of upadacitinib in comparison with the ACT. An added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

The company did not present any data suitable for the derivation of an added benefit in patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior bDMARD therapy. An added benefit of upadacitinib in comparison with the ACT is therefore not proven.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of upadacitinib in comparison with the ACT is summarized in Table 16.

Table 16: Upadacitinib – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy[b]	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	Hint of minor added benefit
Adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior therapy with biologic disease-modifying antirheumatic drugs (bDMARDs)	Switch to another biologic disease-modifying antirheumatic (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab 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. The patient population considered for research question 1 consists of bDMARD-naive patients.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; IL-17: interleukin-17; TNF: tumour necrosis factor

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit for bDMARD-naive patients. For patients who have had an inadequate response or who have been intolerant to a prior therapy with bDMARDs, the company also derived 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.

1. Institute for Quality and Efficiency in Health Care. General methods 6.0 (German version) [online]. 2020 [Accessed: 27.01.2021]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. AbbVie. A Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Participants With Psoriatic Arthritis Who Have an Inadequate Response to at Least One Non-Biologic Disease Modifying Anti-Rheumatic Drug [online]. 2021 [Accessed: 15.02.2021]. URL: https://ClinicalTrials.gov/show/NCT03104400.

4. AbbVie Deutschland. A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Non-Biologic Disease Modifying Anti-Rheumatic Drug (DMARD) – SELECT – PsA 1 [online]. [Accessed: 15.02.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-004130-24.

5. European Medicines Agency. Rinvoq; Assessment report; Procedure No. EMEA/H/C/004760/II/0004 [online]. 2020. URL: https://www.ema.europa.eu/en/medicines/human/EPAR/rinvoq.

6. Abbvie. Rinvoq 15 mg Retardtabletten [online]. 2021 [Accessed: 11.02.2021]. URL: https://www.fachinfo.de.

7. Amgen. Amgevita 20 mg/40 mg Injektionslösung in einer Fertigspritze; Amgevita 40 mg in einem Fertigpen [online]. 2020 [Accessed: 08.02.2021]. URL: https://www.fachinfo.de.

8. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Secukinumab (Psoriasis-Arthritis) – Nutzenbewertung gemäß § 35a SGB V (neue wissenschaftliche Erkenntnisse); Dossierbewertung [online]. 2020 [Accessed: 16.04.2021]. URL: https://www.iqwig.de/download/a20-80_secukinumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

9. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ixekizumab (Psoriasis Arthritis) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2018 [Accessed: 22.06.2018]. URL: https://www.iqwig.de/download/A18-14_Ixekizumab_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

10. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Filgotinib (rheumatoide Arthritis) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 19.01.2021]. URL: https://www.iqwig.de/download/a20-90_filgotinib_nutzenbewertung-35a-sgb-v_v1-0.pdf.

11. Armstrong AW, Banderas B, Foley C et al. Development and psychometric evaluation of the self-assessment of psoriasis symptoms (SAPS) - clinical trial and the SAPS - real world patient-reported outcomes. J Dermatolog Treat 2017; 28(6): 505-514. https://dx.doi.org/10.1080/09546634.2017.1290206.

12. Higgins JP, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. Clin Trials 2008; 5(3): 225-239. https://dx.doi.org/10.1177/1740774508091600.

13. Mease P, Lertratanakul A, Anderson JK et al. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. Ann Rheum Dis 2020.

The full report (German version) is published under https://www.iqwig.de/en/projects/a21-15.html.