IQWiG Reports – Commission No. A21-81

Upadacitinib (psoriatic arthritis) –

Addendum to Commission A21-15[1]

Addendum

Commission: A21-81
Version: 1.0
Status: 22 June 2021

[1] Translation of addendum A21-81 *Upadacitinib (Psoriasis-Arthritis) – Addendum zum Auftrag A21-15* (Version 1.0; Status: 22 June 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.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Upadacitinib (psoriatic arthritis) – Addendum to Commission A21-15

Commissioning agency
Federal Joint Committee

Commission awarded on
8 June 2021

Internal Commission No.
A21-81

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Keywords: Upadacitinib, Arthritis – Psoriatic, Benefit Assessment, NCT03104400

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Abbreviation	Meaning
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD	biologic disease-modifying antirheumatic drug
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying antirheumatic drug
DAPSA	Disease Activity in Psoriatic Arthritis
DMARD	disease-modifying antirheumatic drug
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
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
MDA	minimal disease activity
PASI	Psoriasis Area and Severity Index
PtGADA	Patient Global Assessment of Disease Activity
RCT	randomized controlled trial
SF-36	Short Form 36 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SJC66	swollen joint count 66
SPARCC	Spondyloarthritis Research Consortium of Canada
TJC68	tender joint count 68
VAS	visual analogue scale

1 Background

On 8 June 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-15 (Upadacitinib– Benefit assessment according to §35a Social Code Book V) [1].

For the benefit assessment of upadacitinib, alone or in combination with methotrexate in 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 (research question 1), the pharmaceutical company (hereinafter referred to as "the company") presented the results of the randomized controlled trial (RCT) SELECT-PsA 1 in its dossier [2]. This study was used for the benefit assessment. However, usable data were not available for all patient-relevant outcomes in the company's dossier.

After the oral hearing [3], the G-BA commissioned IQWiG to assess the following data submitted by the company with its written comments [4] under consideration of the information provided in the dossier [2]:

- Health Assessment Questionnaire-Disability Index (HAQ-DI): analyses with a response threshold of 15%
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue): analyses with a response threshold of 15% of the scale range and of ≥ 4 points
- Short Form 36 Health Survey (SF-36): analyses with a response threshold of 15% of the scale range and of ≥ 5 points
- European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS): analyses with a response threshold of 15% of the scale range subject to the subsequent submissions announced by the company at the oral hearing
- Assessment of the outcome "Disease Activity in Psoriatic Arthritis (DAPSA)" with remission and minimal disease activity from the dossier
- Assessment of the following instruments/outcomes, based on the total population, taking into account patients without corresponding symptoms at baseline: Leeds Enthesitis Index (LEI), Leeds Dactylitis Index (LDI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (disease activity), and Psoriasis Area and Severity Index (PASI).

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The SELECT-PsA 1 study is an ongoing study comparing upadacitinib with adalimumab in 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 DMARD (csDMARD). A detailed description of the relevant subpopulation, the characteristics of the study and of the interventions, the data cut-offs and a presentation of the results on the included patient-relevant outcomes can be found in dossier assessment A21-15 [1]. The assessment of the analyses of the SELECT-PsA 1 study subsequently submitted by the company is provided in Section 2.1.

2.1 Results

Outcomes

In dossier assessment A21-15, no usable data were available for some patient-relevant outcomes. The data subsequently submitted by the company and assessed in the present addendum include analyses of the following outcomes:

- Morbidity
  - minimal disease activity (DAPSA ≤ 15)
  - remission (DAPSA ≤ 3.3)
  - enthesitis, recorded with LEI
  - dactylitis, recorded with LDI
  - skin symptoms, recorded with PASI
  - axial involvement, recorded with BASDAI
  - fatigue, recorded with FACIT-Fatigue
  - physical functioning, recorded with HAQ-DI
  - health status, recorded with EQ-5D VAS
- Health-related quality of life
  - SF-36

Minimal disease activity

Results from 2 operationalizations (minimal disease activity [MDA] and DAPSA) are available for the outcome “minimal disease activity”). The results for the MDA were already analysed in dossier assessment A21-15. In contrast to the MDA, the calculation of minimal disease activity on the basis of the DAPSA includes the recording of an inflammatory marker (C-reactive protein [CRP]). The outcome “minimal disease activity” is therefore assessed in an overall consideration of the results for both operationalizations, but primarily on the basis of the MDA.

Enthesitis

Results from 2 operationalizations are available for the outcome "enthesitis" (LEI and Spondyloarthritis Research Consortium of Canada [SPARCC]). The SPARCC was already presented in dossier assessment A21-15. The LEI was developed for the therapeutic indication of psoriatic arthritis [5] and the SPARCC for the therapeutic indication of spondyloarthritis [6]. In the present benefit assessment, the outcome "enthesitis" is therefore assessed in an overall consideration of the operationalizations for both outcomes, but primarily on the basis of the LEI.

Responder analyses

For the outcomes "FACIT-Fatigue" and "HAQ-DI", further responder analyses are available in addition to analyses on the response threshold of 15% of the scale range. According to the methods of the Institute [7], the assessment of the responder analyses is based on the analyses of the response threshold of 15% of the scale range. Analyses on other response thresholds are presented as supplementary information in Appendix A.

Risk of bias

The risk of bias of the results on the BASDAI was rated as low. For the results on the other outcomes, the risk of bias is to be considered as high due to a large proportion of patients who were rated as non-responders due to missing values (> 10% in both treatment arms). For the HAQ-DI this additionally applied because of the large proportion of patients (> 10%) who were not considered in the analysis.

Results

Table 1 and Table 2 summarize the results of the comparison of upadacitinib with adalimumab in biologic DMARD (bDMARD)-naive patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior DMARD therapy. The tables provide a joint presentation of the results from dossier assessment A21-15 and the newly added results from the subsequent submission of the company to allow a comprehensible interpretation. The results from A21-15 are shown in italics for distinction.

Table 1: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: upadacitinib vs. adalimumab (multipage table)[a]

Study Outcome category Outcome	Upadacitinib		Adalimumab		Upadacitinib vs. adalimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[b]
SELECT-PsA 1					
Mortality					
All-cause mortality	*355*	*0 (0)*	*352*	*0 (0)*	–
Morbidity					
Minimal disease activity					
MDA[c, d]	*355*	*173 (48.7)*	*352*	*141 (40.1)*	*1.22 [1.03; 1.44]; 0.021*
Sensitivity analyses:					
ACA[e]	*299*	*173 (57.9)*	*283*	*141 (49.8)*	*1.16 [1.00; 1.35]; 0.05[f]*
NRI[d] with variance correction	*355*	*173 (48.7)*	*352*	*141 (40.1)*	*1.22 [1.01; 1.46]; 0.037[f, g]*
ICA-pc[h] with variance correction	*355*	*201 (56.6)*	*352*	*175 (49.8)*	*1.14 [0.97; 1.32]; 0.104[f, g]*
DAPSA ≤ 15[d, i]	355	204 (57.5)	352	184 (52.3)	1.10 [0.96; 1.25]; 0.177
Remission (DAPSA ≤ 3.3)[d, i]	355	66 (18.6)	352	39 (11.1)	1.68 [1.16; 2.42]; 0.006
Tender joints (TJC68 ≤ 1)[d]	*355*	*164 (46.2)*	*352*	*143 (40.6)*	*1.14 [0.96; 1.34]; 0.139*
Swollen joints (SJC66 ≤ 1)[d]	*355*	*236 (66.5)*	*352*	*208 (59.1)*	*1.12 [1.00; 1.25]; 0.052*
Enthesitis					
LEI = 0[d]	355	255 (71.8)	352	227 (64.5)	1.11 [1.01; 1.23]; 0.037
SPARCC Enthesitis Index =[d]	*268*	*158 (59.0)*	*261*	*143 (54.8)*	*1.07 [0.93; 1.24]; 0.350*
Dactylitis (LDI = 0)[d]	355	295 (83.1)	352	274 (77.8)	1.06 [0.99; 1.14]; 0.104
Fatigue					
FACIT-Fatigue, improvement from baseline by ≥ 7.8 points [15%][d, j]	355	160 (45.1)	352	137 (38.9)	1.16 [0.97; 1.38]; 0.095
Skin symptoms (PASI 100)[d]	355	151 (42.5)	352	134 (38.1)	1.10 [0.92; 1.32]; 0.286
PASI 90[d]	355	181 (51.0)	352	167 (47.4)	1.06 [0.92; 1.23]; 0.421
PASI 75[d]	355	226 (63.7)	352	201 (57.1)	1.10 [0.98; 1.24]; 0.107

Table 1: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: upadacitinib vs. adalimumab (multipage table)[a]

Study Outcome category Outcome	Upadacitinib		Adalimumab		Upadacitinib vs. adalimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[b]
Physical functioning (HAQ-DI, improvement by ≥ 0.45 points [15%])[d, k]	297	166 (55.9)	301	131 (43.5)	1.28 [1.09; 1.51]; 0.003
Health status (EQ-5D VAS improvement by ≥ 15%)[d, l]	355	186 (52.4)	352	146 (41.5)	1.26 [1.08; 1.48]; 0.004
Health-related quality of life					
SF-36 PCS (improvement by ≥ 9.4 points [15%])[d, m]	355	180 (50.7)	352	135 (38.4)	1.32 [1.12; 1.57]; 0.001
SF-36 MCS (improvement by ≥ 9.6 points [15%])[d, n]	355	96 (27.0)	352	59 (16.8)	1.63 [1.22; 2.18]; < 0.001
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*

a. Results from assessment A21-15 [1] are presented in italics.
b. 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).
c. 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.
d. Missing values imputed using NRI.
e. Analysis is exclusively based on patients with complete observation.
f. Institute's calculation, asymptotic.
g. Institute's calculation, estimation of variance according to the dataset re-sizing approach (approach W3 in [8]).
h. In both treatment groups, the missing values are imputed according to the observed risk in the control group.
i. The sum score of the DAPSA is recorded as follows: SJC66 + TJC68 + pain (measured by NRS with a range from 0 to 10) + PtGADA (measured by NRS with a range from 0 to 10) + CRP (in mg/dL). The DAPSA is an open-ended scale starting at 0, with higher scores reflecting more severe disease activity.
j. Scale range from 0 to 52.
k. Scale range from 0 to 3.
l. Scale range from 0 to 100.
m. Scale range from 7 to 63.
n. Scale range from 6 to 64.

Table 1: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: upadacitinib vs. adalimumab (multipage table)[a]

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[b]
ACA: available case analysis; AE: adverse event; BSA: body surface area; CI: confidence interval; DAPSA: Disease Activity in Psoriatic Arthritis; DMARD: disease-modifying antirheumatic drug; EQ-5D: European Quality of Life-5 Dimensions; 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; MCS: Mental Component Summary; MDA: minimal disease activity; N: number of analysed patients; n: number of patients with (at least one) event; NRI: non-responder imputation; NRS: numeric rating scale; PASI: Psoriasis Area and Severity Index; PCS: Physical Component Summary; 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; VAS: visual analogue scale					

Table 2: Results (morbidity, continuous) – RCT, direct comparison: upadacitinib vs. adalimumab[a]

Study Outcome category Outcome	Upadacitinib			Adalimumab			Upadacitinib vs. adalimumab
	N[b]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)[c]	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)[c]	MD [95% CI]; p-value[c]
SELECT-PsA 1							
Morbidity							
Morning stiffness[d]							
Severity[e]	*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[f]	*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]*
Axial involvement (BASDAI)[d]	341	5.68 (2.19)	−2.78 (0.11)	348	5.39 (2.19)	−2.33 (0.10)	−0.45 [−0.72; −0.19]; < 0.001 Hedges' g: −0.24 [−0.39; −0.09]
Pain (pain NRS)[d]	*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)[d]	*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)[g]	*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. Results from assessment A21-15 [1] are presented in italics.
b. 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.
c. 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.
d. 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.
e. Recorded using the BASDAI item 5.
f. Recorded using the BASDAI item 6.
g. 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

In the following, the results of those outcomes are interpreted for which the company subsequently presented analyses. Based on the available data, at most an indication, e.g. of an added benefit, can be derived for the outcome "BASDAI", and at most a hint for all other outcomes.

Morbidity

Minimal disease activity

Minimal disease activity was operationalized using the MDA and the DAPSA (≤ 15). The assessment was primarily based on the MDA.

There was no statistically significant difference between the study arms for minimal disease activity recorded using the DAPSA (≤ 15).

For the minimal disease activity recorded using the MDA, dossier assessment A21-15 showed a hint of an added benefit of upadacitinib compared with adalimumab.

Overall, there is a hint of an added benefit of upadacitinib in comparison with adalimumab for minimal disease activity.

Remission (DAPSA ≤ 3.3)

A statistically significant difference was shown in favour of upadacitinib for the outcome "remission" recorded with the DAPSA ≤ 3.3. This resulted in a hint of an added benefit of upadacitinib in comparison with adalimumab.

Enthesitis

Enthesitis was operationalized using the LEI and SPARCC. The assessment was primarily based on the LEI.

A statistically significant difference in favour of upadacitinib was shown for enthesitis recorded using the LEI. The effect in this non-serious/non-severe outcome was no more than marginal, however. This resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven.

For enthesitis, recorded using the SPARCC, dossier assessment A21-15 showed no difference between the treatment arms.

Overall, there is no hint of an added benefit of upadacitinib in comparison with adalimumab for enthesitis; an added benefit is therefore not proven.

Dactylitis (LDI)

There was no statistically significant difference between the study arms for dactylitis recorded using the LDI. This resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven.

Axial involvement (BASDAI)

A statistically significant difference in favour of upadacitinib was shown for axial involvement recorded using the BASDAI. 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.

FACIT-Fatigue

There was no statistically significant difference between the study arms for the FACIT-Fatigue. This resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven.

PASI

No statistically significant difference between the study arms was shown for the PASI 100 as well as for the PASI 90 and the PASI 75. 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.

Physical functioning (HAQ-DI)

Based on the responder analyses on the response threshold of 15% of the scale range, a statistically significant difference in favour of upadacitinib was shown for physical functioning recorded with the HAQ-DI. The effect in this non-serious/non-severe outcome was no more than marginal, however. This resulted in no hint of an added benefit of upadacitinib in comparison with adalimumab; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

Based on the responder analyses on the response threshold of 15% of the scale range, a statistically significant difference in favour of upadacitinib was shown for health status recorded with the EQ-5D VAS. The effect in this non-serious/non-severe outcome was no more than marginal, however. 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

SF-36

Based on the responder analyses on the response threshold of 15% of the scale range there was a statistically significant difference in favour of upadacitinib for the physical and the mental component summary of the SF-36. In each case, this resulted in a hint of an added benefit of upadacitinib in comparison with adalimumab.

Subgroups

The data subsequently submitted by the company do not contain any investigations on effect modifications.

2.2 Probability and extent of added benefit

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.1 (see Table 3).

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.

Remission

There was a hint of an added benefit for the outcome "DAPSA ≤ 3.3". The DAPSA sum score includes the components of tender joint count 68 (TJC68), swollen joint count 66 (SJC66), Patient Global Assessment of Disease Activity (PtGADA) and CRP.

The company's dossier did not contain summarizing information on the severity of psoriatic arthritis at baseline. However, an examination of TJC68, SJC66 and PtGADA shows a high number of affected joints or strong patient-reported disease activity with values in the upper scale ranges (see Table 8 of dossier assessment A21-15 [1]). Therefore, the patients' disease activity was rated as serious/severe and the achievement of a DAPSA ≤ 3.3 was assigned to this category accordingly.

Table 3: Extent of added benefit at outcome level: upadacitinib vs. adalimumab (multipage table)[a]

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[b]**	**Derivation of extent[c]**
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][d];* *p = 0.021* *probability: "hint"*	*Outcome category: serious/severe symptoms/late complications* *$0.90 \leq CI_u < 1.00$* *added benefit, extent: "minor"*
Remission (DAPSA ≤ 3.3)	18.6% vs. 11.1% RR: 1.68 [1.16; 2.42] RR: 0.60 [0.41; 0.86][d]; p = 0.006 probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
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 (LEI = 0)	71.8% vs. 64.5% RR: 1.11 [1.01; 1.23] RR: 0.90 [0.81; 0.99][d]; p = 0.037	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$[e] lesser benefit/added benefit not proven
Dactylitis (LDI = 0)	83.1% vs. 77.8% RR: 1.06 [0.99; 1.14]; p = 0.104	Lesser benefit/added benefit not proven
Axial involvement (BASDAI)	−2.78 vs. −2.33 MD: −0.45 [−0.72; −0.19]; p < 0.001 Hedges' g: −0.24 [−0.39; −0.09][f]	Lesser benefit/added benefit not proven
Fatigue (FACIT-Fatigue, improvement from baseline by ≥ 7.8 points [15%])	45.1% vs. 38.9% RR: 1.16 [0.97; 1.38]; p = 0.095	Lesser benefit/added benefit not proven
Skin symptoms (PASI 100)	42.5% vs. 38.1% RR: 1.10 [0.92; 1.32]; p = 0.286	Lesser benefit/added benefit not proven

Table 3: Extent of added benefit at outcome level: upadacitinib vs. adalimumab (multipage table)[a]

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**[b]	**Derivation of extent**[c]
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]*[e]	*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]*[e]	*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]*[e]	*Lesser benefit/added benefit not proven*
Physical functioning (HAQ-DI, improvement by ≥ 0.45 points [15%])	55.9% vs. 43.5% RR: 1.28 [1.09; 1.51] RR: 0.78 [0.66; 0.92][d]; p = 0.003	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[e]
EQ-5D VAS (improvement by ≥ 15%)	52.4% vs. 41.5% RR: 1.26 [1.08; 1.48] RR: 0.79 [0.68; 0.93][d]; p = 0.004	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[e]
Health-related quality of life		
SF-36 PCS (improvement by ≥ 9.4 points [15%])	50.7% vs. 38.4% RR: 1.32 [1.12; 1.57] RR: 0.76 [0.64; 0.89][d]; p = 0.001 Probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
SF-36 MCS (improvement by ≥ 9.6 points [15%])	27.0% vs. 16.8% RR: 1.63 [1.22; 2.18] RR: 0.61 [0.46; 0.82][d]; p < 0.001 Probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"

Table 3: Extent of added benefit at outcome level: upadacitinib vs. adalimumab (multipage table)[a]

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[b]**	**Derivation of extent[c]**
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. Results from assessment A21-15 [1] are presented in italics.
b. Probability provided if a statistically significant and relevant effect is present.
c. 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).
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
f. 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; DAPSA: Disease Activity in Psoriatic Arthritis; 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; MCS: Mental Component Summary; MD: mean difference; MDA: minimal disease activity; NRS: numeric rating scale; PASI: Psoriasis Area and Severity Index; PCS: Physical Component Summary; 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

Table 4: Positive and negative effects from the assessment of upadacitinib in comparison with adalimumab

Positive effects	Negative effects
Serious/severe symptoms/late complications: minimal disease activity ▪ MDA: hint of an added benefit – extent: "minor"	-
Serious/severe symptoms/late complications: remission according to DAPSA: hint of an added benefit – extent: "considerable"	
Health-related quality of life: SF-36 MCS and SF-36 PCS, each hint of an added benefit – extent: "considerable"	
The results presented in **bold** result from the analyses subsequently submitted by the company with its written comments. DAPSA: Disease Activity in Psoriatic Arthritis; MCS: Mental Component Summary; MDA: minimal disease activity; PCS: Physical Component Summary; SF-36: Short Form 36 Health Survey	

The data subsequently submitted by the company changed the conclusion on the added benefit of upadacitinib compared with dossier assessment A21-15 [1].

Only positive effects of upadacitinib were shown. In the categories of serious/severe symptoms/late complications and health-related quality of life, these are several hints of an added benefit of predominantly considerable extent.

In summary, there is a hint of considerable 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.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure changed the conclusion on the added benefit of upadacitinib from dossier assessment A21-15 for 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). For research question 2 (patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior bDMARD therapy), there is no change in comparison with dossier assessment A21-15.

The following Table 5 shows the result of the benefit assessment of upadacitinib under consideration of dossier assessment A21-15 and the present addendum.

Table 5: 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 **considerable** 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.

The results presented in **bold** result from the analyses subsequently submitted by the company with its written comments.

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 G-BA decides on the added benefit.

3 References

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Appendix A – Responder analyses

Table 6: Results (morbidity, health-related quality of life, dichotomous) – RCT, direct comparison: upadacitinib vs. adalimumab

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					
Morbidity					
FACIT-Fatigue, improvement from baseline by ≥ 4 points[b, c]	355	202 (56.9)	352	180 (51.1)	1.11 [0.97; 1.28]; 0.125
Health-related quality of life					
SF-36 PCS (improvement by ≥ 5 points)[b, d]	355	246 (69.3)	352	194 (55.1)	1.26 [1.12; 1.41]; < 0.001
SF-36 MCS (improvement by ≥ 5 points)[b, e]	355	152 (42.8)	352	115 (32.7)	1.31 [1.08; 1.59]; 0.006

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. Missing values imputed using NRI.
c. Scale range from 0 to 52.
d. Scale range from 7 to 63.
e. Scale range from 6 to 64.

CI: confidence interval; DMARD: disease-modifying antirheumatic drug; FACIT: Functional Assessment of Chronic Illness Therapy; MCS: Mental Component Summary; N: number of analysed patients; n: number of patients with (at least one) event; PCS: Physical Component Summary; RCT: randomized controlled trial; RR: relative risk; SF-36: Short Form 36 Health Survey