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Abrocitinib (atopic dermatitis) –

Addendum to Commission A22-06[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse events
EASI	Eczema Area and Severity Index
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IGA	Investigator Global Assessment
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed model for repeated measures
NRS	numerical rating scale
POEM	Patient-Oriented Eczema Measure
RCT	randomized controlled trial
SCORAD	SCORing Atopic Dermatitis
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 24 May 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments on Commission A22-06 (Abrocitinib – benefit assessment according to §35a Social Code Book V) [1].

For the benefit assessment of abrocitinib in adults with moderate to severe atopic dermatitis in adults who are candidates for systemic treatment, the pharmaceutical company (hereinafter referred to as the "company") presented in its dossier [2] results from the randomized controlled trial (RCT) JADE DARE. This study was used for the benefit assessment. As part of the commenting procedure [3], the company submitted further explanations and analyses.

The G-BA commissioned IQWiG with the assessment of the following analyses, taking into account the information provided in the dossier:

- analyses of SCORing Atopic Dermatitis (SCORAD) 100 and Eczema Area and Severity Index (EASI) 100
- analyses of the Patient-Oriented Eczema Measure [POEM] 0
- analysis of the European Quality of Life Questionnaire – 5 Dimensions (EQ-5D) visual analogue scale (VAS) with the response criterion of improvement by ≥ 15 points
- analysis of pain (Skin Pain numerical rating scale [NRS]), taking into account the 15% response criterion
- reassessment of itching (Peak Pruritus NRS) with the response criterion of improvement by ≥ 4 points

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 JADE DARE study is a randomized double-blind RCT comparing abrocitinib and dupilumab. Dossier assessment A22-06 [1] presents a detailed description of the study population, the characteristics of both the study and the interventions, and the results on the included patient-relevant outcomes. The JADE DARE study's analyses commissioned by the G-BA are evaluated in the sections below.

2.1 Outcomes

In the present addendum, analyses of the following outcomes are evaluated:

- symptoms – remission (recorded with the EASI 100 and SCORAD 100)
- symptoms – itching (surveyed using Peak Pruritus NRS)
- symptoms – pain (surveyed using Skin Pain NRS)
- patient-reported symptoms (surveyed using POEM)
- health status (recorded with the EQ-5D VAS)

Notes regarding outcomes

Symptoms – itching (Peak Pruritus NRS)

For the outcome of itching (Peak Pruritus NRS), responder analyses for improvement by ≥ 4 points at Week 26 are presented as supplementary information. This response criterion is deemed relevant for patients who cannot reach (nearly) complete freedom from symptoms. Given the available evidence, however, the operationalization of Peak Pruritus NRS 0–1 at Week 26 continued to be used for the benefit assessment because, in the present therapeutic indication, (nearly) complete absence of itching is to be strived for and represents the treatment goal, which is indeed generally achievable with the systemic continuous therapies of abrocitinib or dupilumab (see Section 2.4.1. of dossier assessment A22-06 [1]).

Neither for the analysis of improvement by ≥ 4 points nor for the analysis of Peak Pruritus NRS 0–1 is there a statistically significant difference between abrocitinib and dupilumab.

Symptoms – pain (Skin Pain NRS)

For the outcome of pain, surveyed with Skin Pain NRS, the company's dossier presents an analysis of improvement by ≥ 4 points. Dossier assessment A22-06 disregarded this analysis for having presumably been specified post hoc. According to the IQWiG General Methods [4], analyses specified post hoc are to be taken into account only if the response criterion equals exactly 15% of the scale range. Dossier assessment A22-06 included the analyses submitted using a mixed linear model for repeated measures (MMRM). In its comments, the company clarified that the analysis it presented was predefined. For this reason, the benefit assessment is performed using the responder analysis submitted by the company.

Health status (EQ-5D VAS)

In dossier assessment A22-06, the analysis presented in the dossier was assumed to represent an analysis on deterioration of health status (EQ-5D VAS). During the commenting procedure [3], the company reported that the corresponding responder analysis had been described incorrectly and the analysis presented in the dossier concerned improvement (increase) by ≥ 15 points from baseline. Accordingly, 13 of 357 patients (3.6%) in the intervention arm and 6 of 361 patients (1.7%) in the comparator arm achieved an improvement by ≥ 15 points at Week 26.

According to the available documents, however, among patients whose score changed from baseline to Week 26 (303 patients in in the intervention arm and the 323 in the comparator arm) 25% showed improvements by equal to or greater than 24 and 25 points, respectively. Hence, at least these patients achieved an improvement in health status by ≥ 15 points. Consequently, it is impossible for the analysis presented by the company to represent the analysis of improvement of health status. Due to the expected course of disease in the present therapeutic indication, an analysis of improvement of health status is primarily relevant. Therefore, the analyses with MMRM are used for the assessment in the present addendum, as was the case in dossier assessment A22-06. The analysis presented by the company is presented in Appendix A. Like in the MMRM analysis, no statistically significant difference between treatment groups is found.

2.2 Risk of bias

For the results of the outcome of remission (EASI 100), the risk of bias has already been assessed in Section 2.4.2 of dossier assessment A22-06 [1]. Since IQWiG analyses showed consistent results, the certainty of results was not reduced despite a high risk of bias.

The risk of bias is rated as high for of results of each of the outcomes of remission (SCORAD 100), pain (Skin Pain NRS), and patient-reported symptoms (POEM 0). In each case, this is due to the proportion of replaced values being either unclear or high and differential (see Table 1). Furthermore, for the outcome of pain (Skin Pain NRS), the analysis disregards over 10% of patients.

The company did not submit any sensitivity analyses on the subsequently submitted analyses. Therefore, IQWiG conducted calculations using various replacement strategies, and their results were qualitatively consistent with the presented results. Due to said consistency as well as the larger proportion of values replaced as non-response in the intervention arm (see Table 1), the certainty of results for the outcomes of remission (SCORAD 100) and patient-reported symptoms (POEM 0) is not downgraded despite high risk of bias, and for these outcomes, at most indications, e.g. of added benefit, can be derived.

For the outcome of pain (Skin Pain NRS), in contrast, the additional high proportion of disregarded values caused a downgrading of the certainty of results, and at most a hint, e.g. of added benefit, can be derived for this outcome.

Table 1: Overview of replaced values in responder analyses for individual outcomes of the JADE DARE study for the purposes of assessing the risk of bias on outcome level

Outcome **Time point (replacement strategy)**	**Abrocitinib + TCS** **N = 362**	**Dupilumab + TCS** **N = 365**
Remission (SCORAD 100)		
N* (%[a]) in analysis (NRI[b])	362 (100)	365 (100)
Replaced values (NRI), n (%[c])	62 (17.1)	42 (11.5)
Itching (Peak Pruritus NRS, improvement by ≥ 4 points[d])		
N* (%[a]) in analysis (NRI[b])[e]	357 (98.6)	364 (99.7)
Replaced values (NRI), n (%[c])	46 (12.9)	37 (10.2)
Pain (Skin Pain NRS, improvement by ≥ 4 points[d])		
N* (%[a]) in analysis (NRI[b])[e]	316 (87.3)	325 (89.0)
Replaced values (NRI), n (%[c])	53 (16.8)	41 (12.6)
Patient-reported symptoms (POEM 0)		
N* (%[a]) in analysis (NRI[b])[f]	359 (99.2)	365 (100)
Replaced values (NRI), n (%[c])	ND[g]	ND[g]

a. Percentage based on N, the number of randomized patients.
b. Values after treatment discontinuation or rescue therapy as well as missing values were likewise replaced using non-response imputation.
c. Percentage based on N*, the number of analysed patients.
d. Improvement is defined as a decrease by ≥ 4 points from baseline, at a scale range of 0 to 10. Lower (decreasing) values indicate an improvement of symptoms.
e. The analysis included patients with a baseline score ≥ 4 points.
f. The analysis included patients with a baseline score ≥ 1 point.
g. The number of replaced values equals a maximum of 60 (16.7%) in the intervention arm and a maximum of 45 (12.3%) in the control arm.

N: number of randomized patients; N*: number of analysed patients; n: number of replaced values; NRI: non-response imputation; NRS: numerical rating scale; POEM: Patient-Oriented Eczema Measure; SCORAD: SCORing Atopic Dermatitis; TCS: topical corticosteroids

2.3 Results

Table 2 summarizes the results of the analyses commissioned by the G-BA for the comparison of abrocitinib with dupilumab in adults with moderate to severe atopic dermatitis who are candidates for systemic treatment.

Table 2: Results (morbidity) – RCT, direct comparison: abrocitinib versus dupilumab

Study Outcome category Outcome	Abrocitinib N	Abrocitinib Patients with event n (%)	Dupilumab N	Dupilumab Patients with event n (%)	Abrocitinib vs. dupilumab RR [95% CI]; p-value[a]
JADE DARE					
Morbidity[b,c]					
Symptoms					
Remission (EASI 100)	362	79 (21.8)	365	50 (13.7)	1.59 [1.15; 2.20]; 0.005
Remission (SCORAD 100)	362	37 (10.2)	365	22 (6.0)	1.70 [1.02; 2.82]; 0.041
Itching (Peak Pruritus NRS, improvement by ≥ 4 points[d]), presented as supplementary information	*357*	*241 (67.5)*	*364*	*229 (62.9)*	*1.07 [0.96; 1.19]; 0.198*
Pain (Skin Pain NRS, improvement by ≥ 4 points[d])	316	205 (64.9)	325	202 (62.2)	1.04 [0.93; 1.17]; 0.475
Patient-reported symptoms (POEM 0[e])	359	49 (13.6)	365	26 (7.1)	1.92 [1.22; 3.01]; 0.005

a. Cochran-Mantel-Haenszel method, stratified by disease severity at baseline (IGA = 3 vs. IGA = 4)
b. Analysis at Week 26.
c. Values after treatment discontinuation or rescue therapy as well as missing values were replaced using non-response imputation.
d. Improvement is defined as a decrease by ≥ 4 points from baseline, at a scale range of 0 to 10. Lower (decreasing) values indicate an improvement of symptoms. The analysis included patients with a baseline score ≥ 4 points.
e. The analysis included patients with a baseline score ≥ 1 points.

CI: confidence interval; EASI: Eczema Area and Severity Index; IGA: Investigator Global Assessment; N: number of analysed patients; NRS: numerical rating scale; POEM: Patient-Oriented Eczema Measure; RCT: randomized controlled trial; RR: relative risk; SCORAD: SCOring Atopic Dermatitis

Based on the available data, at most indications, e.g. of an added benefit, can be derived for all outcomes except the outcome of pain (Skin Pain NRS). For the outcome of pain (Skin Pain NRS), at most a hint, e.g. of an added benefit, can be derived (see Section 2.2).

Morbidity

Symptoms – remission (EASI 100 and SCORAD 100)

For the outcome of remission, surveyed using EASI 100 and SCORAD100, there is a statistically significant difference in favour of abrocitinib in comparison with dupilumab. This results in an indication of added benefit of abrocitinib in comparison with dupilumab for each of them.

Pain (Skin Pain NRS, improvement by ≥ 4 points)

No statistically significant difference between treatment arms was shown for the outcome of pain (Skin Pain NRS, improvement by ≥ 4 points). This results in no hint of an added benefit

of abrocitinib in comparison with dupilumab; an added benefit is therefore not proven for this outcome.

Patient-reported symptoms (POEM 0)

A statistically significant difference in favour of abrocitinib in comparison with dupilumab was shown for the outcome of patient-reported symptoms (POEM 0). However, there was an effect modification by the characteristic of age. This results in an indication of added benefit for patients ≥ 40 years of age. For patients < 40 years of age, there is no hint of an added benefit of abrocitinib in comparison with dupilumab; an added benefit is therefore not proven for patients < 40 years of age for this outcome (see Section 2.4).

2.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- sex (female versus male)
- age (< 40 years versus ≥ 40 years)
- disease severity (Investigator Global Assessment [IGA] 3 versus IGA 4)

In the commenting procedure, the company submitted subgroup analyses on the outcomes of remission (EASI 100), remission (SCORAD 100), and patient-reported symptoms (POEM 0). Still, no (usable) subgroup analyses are available for the analyses used in dossier assessment A22-06 on the outcomes of itching (Peak Pruritus NRS 0–1) and health status (EQ-5D VAS, MMRM analysis), on the specific adverse events (AEs) of infections, eye disorders (System Organ Class [SOC], AEs), or on nervous system disorders (SOC, AEs). For the outcome of pain (Skin Pain NRS, improvement by ≥ 4 points), the company had already submitted subgroup analyses in its dossier. In dossier assessment A22-06, these analyses were disregarded because the analysis of improvement by ≥ 4 points was assumed to have been specified post hoc (see Section 2.1).

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least 1 subgroup.

For the outcomes for which subgroup analyses are available, Table 3 presents the described selection of subgroup results regarding the comparison of abrocitinib with dupilumab.

Table 3: Subgroups (morbidity) – RCT, direct comparison: abrocitinib versus dupilumab

Study Outcome Characteristic Subgroup	Abrocitinib N	Abrocitinib Patients with event n (%)	Dupilumab N	Dupilumab Patients with event n (%)	Abrocitinib vs. dupilumab RR [95% CI]	Abrocitinib vs. dupilumab p-value[a]
JADE DARE						
Morbidity[b,c]						
Patient-reported symptoms (POEM 0[d])						
Age						
< 40 years	227	22 (9.7)	247	19 (7.7)	1.26 [0.70; 2.27]	0.514
≥ 40 years	132	27 (20.5)	118	7 (5.9)	3.45 [1.56; 7.62]	< 0.001
Total					Interaction:	0.009[e]

a. Unstratified.
b. Analysis at Week 26.
c. Values after treatment discontinuation or rescue therapy as well as missing values were replaced using non-response imputation.
d. The analysis included patients with a baseline score ≥ 1 point.
e. Logistical regression model with corresponding interaction term; unstratified.

CI: confidence interval; n: number of patients with (at least 1) event; N: number of analysed patients; POEM: Patient-Oriented Eczema Measure; RCT: randomized controlled trial; RR: relative risk

Patient-reported symptoms (POEM 0)

For the outcome of patient-reported symptoms (POEM 0), there was an effect modification by the characteristic of age. A statistically significant difference in favour of abrocitinib in comparison with dupilumab was found for patients ≥ 40 years of age, whereas no statistically significant difference was shown for patients < 40 years of age. This results in an indication of added benefit of abrocitinib versus dupilumab for patients ≥ 40 years of age. For patients < 40 years of age, there is no hint of an added benefit of abrocitinib in comparison with dupilumab; an added benefit is therefore not proven for patients < 40 years of age for this outcome.

2.5 Probability and extent of added benefit

On the basis of the results presented in Section 2.3 and those of dossier assessment A22-06, the extent of the respective added benefit was estimated at outcome level (see Table 4).

Determination of the outcome category for symptom outcomes

For the symptoms outcomes below, the documents do not state directly whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms – remission (EASI 100)

The outcome of remission (EASI 100) has already been allocated to the category of serious/severe symptoms / late complications (see Section 2.5.1 of dossier assessment A22-06 [1]).

Symptoms – remission (SCORAD 100)

The allocation of the outcome of remission (SCORAD 100) to an outcome category depends on the patients' initial situation, particularly on the severity and the grade of impairment from symptoms. Therefore, the baseline data are used.

JADE DARE participants exhibited a median baseline SCORAD score of 66.4 in the intervention arm and 65.2 in the comparator arm, both being above 50. The median SCORAD scores are therefore in the serious range [5,6]. Consequently, the outcome of remission (SCORAD 100) is allocated to the category of serious/severe symptoms / late complications.

Patient-reported symptoms (POEM 0)

The analysis of POEM 0 for patient-reported symptoms is allocated to the category of serious/severe symptoms / late complications for the same reason as the analysis of POEM 0-2 (see Section 2.5.1 of dossier assessment A22-06 [1]).

Table 4: Extent of added benefit at outcome level: abrocitinib versus dupilumab (multipage table)

Outcome category **Outcome**	**Abrocitinib vs. dupilumab** **Event rate (%) or change at Week 26 (mean)** **Effect estimation [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0.6% vs. 0% RR: –	Lesser/added benefit not proven
Morbidity		
Remission (EASI 100)	21.8% vs. 13.7% RR: 1.59 [1.15; 2.20] RR: 0.63 [0.45; 0.87][c] p = 0.005 Probability: indication	Outcome category: serious/severe symptoms / late complications $0.75 \leq CI_u < 0.90$ Added benefit; extent: considerable
Remission (SCORAD 100)	10.2% vs. 6.0% RR: 1.70 [1.02; 2.82] RR: 0.59 [0.35; 0.98][c] p = 0.041 Probability: indication	Outcome category: serious/severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Added benefit, extent: minor
Itching (Peak Pruritus NRS 0–1)	38.4% vs. 31.2% RR: 1.23 [0.99; 1.52] p = 0.058	Lesser/added benefit not proven

Table 4: Extent of added benefit at outcome level: abrocitinib versus dupilumab (multipage table)

Outcome category **Outcome**	**Abrocitinib vs. dupilumab** **Event rate (%) or change at Week 26 (mean)** **Effect estimation [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
Sleep disturbances (MOS Sleep Scale, improvement by ≥ 15 points)		
SPI I	36.2% vs. 32.2% RR: 1.12 [0.92; 1.37] p = 0.264	Lesser/added benefit not proven
SPI II	38.4% vs. 38.5% RR: 1.00 [0.83; 1.20] p = 0.972	Lesser/added benefit not proven
Pain (Skin Pain NRS, improvement by ≥ 4 points)	64.9% vs. 62.2% RR: 1.04 [0.93; 1.17] p = 0.475	Lesser/added benefit not proven
Patient-reported symptoms (POEM 0)		
Age		
< 40 years	9.7% vs. 7.7% RR: 1.26 [0.70; 2.27] p = 0.514	Lesser/added benefit not proven
≥ 40 years	20.5% vs. 5.9% RR: 3.45 [1.56; 7.62] RR: 0.29 [0.13; 0.64][c] p < 0.001 Probability: indication	Outcome category: serious/severe symptoms / late complications CI_u < 0.75, risk ≥ 5% Added benefit, extent: major
Health status (EQ-5D VAS)	13.48 vs. 14.30 MD: -0.82 [-2.91; 1.28] p = 0.445	Lesser/added benefit not proven
Health-related quality of life		
DLQI 0–1	38.3% vs. 31.6% RR: 1.21 [0.99; 1.48] p = 0.060	Lesser/added benefit not proven
Side effects		
SAEs	1.7% vs. 1.6% RR: 1.01 [0.33; 3.10] p = 0.989	Greater/lesser harm not proven
Discontinuation due to AEs	2.5% vs. 2.5% RR: 1.01 [0.40; 2.51] p = 0.986	Greater/lesser harm not proven
Infections (AEs)	30.4% vs. 29.9% RR: 1.02 [0.82; 1.27] p = 0.916	Greater/lesser harm not proven

Table 4: Extent of added benefit at outcome level: abrocitinib versus dupilumab (multipage table)

Outcome category **Outcome**	**Abrocitinib vs. dupilumab** **Event rate (%) or change at Week 26 (mean)** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Serious infections (SAEs)	0.8% vs. 0% RR: –	Greater/lesser harm not proven
Conjunctivitis (AEs)	2.2% vs. 9.6% RR: 0.23 [0.11; 0.49] p < 0.001 Probability: indication	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm, extent: considerable
Eye disorders (AEs)	4.7% vs. 7.7% RR: 0.61 [0.34; 1.10] p = 0.103	Greater/lesser harm not proven
Nervous system disorders (AEs)	19.3% vs. 9.0% RR: 2.14 [1.45; 3.15] RR: 0.47 [0.32; 0.69][c] p < 0.001 Probability: indication	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: considerable
Nausea (AEs)	19.3% vs. 2.2% RR: 8.82 [4.31; 18.07] RR: 0.11 [0.06; 0.23][c] p < 0.001 Probability: indication	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: considerable
Acne (AEs)	12.7% vs. 2.7% RR: 4.64 [2.38; 9.05] RR: 0.22 [0.11; 0.42][c] p < 0.001 Probability: indication	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: considerable

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category and scale level of the outcome, estimations of effect size are made with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).
c. IQWiG calculation; reversed direction of effect to enable use of limits to derive the extent of added benefit.

AE: adverse event; CI: confidence interval; CI_L: lower limit of confidence interval; CI_u: upper limit of confidence interval; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; MD: mean difference; MOS: Medical Outcome Study; NRS: numerical rating scale; POEM: Patient-Oriented Eczema Measure; RR: relative risk; SAE: serious adverse event; SCORAD: SCORing Atopic Dermatitis; SPI: Sleep Problem Index; VAS: visual analogue scale

Table 5 summarizes the results accounted for in the overall conclusion on the extent of added benefit.

Table 5: Favourable and unfavourable effects from the assessment of abrocitinib in comparison with dupilumab

Favourable effects	**Unfavourable effects**
Serious/severe symptoms / late complications ▪ Remission (EASI 100): indication of an added benefit – extent: considerable ▪ Remission (SCORAD 100): indication of an added benefit – extent: minor ▪ Patient-reported symptoms (POEM 0) ▫ Age ≥ 40 years: indication of an added benefit – extent: major	–
Non-serious/non-severe side effects ▪ Conjunctivitis (AEs): indication of lesser harm – extent: considerable	Non-serious/non-severe side effects ▪ Nervous system disorders (AEs): indication of greater harm – extent: considerable ▪ Nausea (AEs): indication of greater harm – extent: considerable ▪ Acne (AEs): indication of greater harm – extent: considerable
AE: adverse event; EASI: Eczema Area and Severity Index; POEM: Patient-Oriented Eczema Measure	

The data subsequently submitted by the company changed the conclusion on the added benefit of abrocitinib drawn in dossier assessment A22-06 [1].

Overall, both favourable and unfavourable effects were found for abrocitinib in comparison with dupilumab. For the outcome of remission, there is an indication of considerable added benefit in EASI 100 as well as an indication of minor added benefit in SCORAD 100. For patients ≥ 40 years of age, there is an additional indication of major added benefit for the outcome of patient-reported symptoms. Further, an indication of lesser harm of considerable extent was found for the AE of conjunctivitis. These effects are offset by indications of greater harm, each of considerable extent, in the AEs of nervous system disorders, nausea, and acne.

In summary, for adults < 40 years of age with moderate-to-severe atopic dermatitis who are candidates for systemic treatment, there is an indication of considerable added benefit of abrocitinib in comparison with the appropriate comparator therapy (ACT) of dupilumab. For adults ≥ 40 years of age with moderate-to-severe atopic dermatitis who are candidates for systemic treatment, there is an indication of major added benefit of abrocitinib in comparison with the ACT of dupilumab.

2.6 Summary

The data subsequently submitted by the company in the commenting procedure change the conclusion on the added benefit of abrocitinib drawn in dossier assessment A22-06 for patients ≥ 40 years of age. For patients < 40 years of age, there is no change from dossier assessment A22-06.

Table 6 below shows the result of the benefit assessment of abrocitinib, taking into account dossier assessment A22-06 and the present addendum.

Table 6: Abrocitinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Moderate-to-severe atopic dermatitis in adults who are candidates for systemic treatment[b]	Dupilumab (if applicable in combination with TCS and/or TCI)	▪ < 40 years: indication of considerable added benefit[c] ▪ ≥ 40 years: indication of major added benefit[c]

a. Presented is the ACT specified by the G-BA.
b. As per approval, the therapeutic indication comprises patients who are candidates for systemic treatment. For the purposes of determining the ACT, the target population has been narrowed down to adults with moderate-to-severe atopic dermatitis who are indicated for long-term/continuous systemic therapy because the drug abrocitinib is to be administered as continuous therapy and therefore represents an option only for patients indicated for long-term/continuous systemic therapy.
c. Abrocitinib can be used as monotherapy or with other drugs for topical use in atopic dermatitis. No data are available on monotherapy. It remains unclear whether the observed effects are transferable to patients receiving only monotherapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TCI: topical calcineurin inhibitors; TCS: topical corticosteroids

The G-BA decides on the added benefit.

3 References

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Appendix A – Responder analysis on health status (EQ-5D VAS) presented by the company

Table 7: Results presented as supplementary information (morbidity) – RCT, direct comparison: abrocitinib versus dupilumab

Study Outcome category Outcome	Abrocitinib		Dupilumab		Abrocitinib vs. dupilumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
JADE DARE					
Morbidity[b,c]					
Health status (EQ-5D VAS[d])	357	13 (3.6)	361	6 (1.7)	2.20 [0.85; 5.71]; 0.104

a. Cochran-Mantel-Haenszel method, stratified by disease severity at baseline (IGA = 3 vs. IGA = 4).
b. Analysis at Week 26.
c. Values after treatment discontinuation or rescue therapy as well as missing values were replaced using non-response imputation (abrocitinib: 58 [16.2%] vs. dupilumab: 40 [11.1%]).
d. Reported by the company as improvement by ≥ 15 points; however, this analysis presumably represents the analysis of deterioration in health status; see Section 2.1. Improvement is defined as an increase by ≥ 15 points from baseline at a scale range of 0 to 100. Higher (increasing) scores indicate improved symptoms. The analysis included patients with a baseline score ≥ 15 points.

CI: confidence interval; IGA: Investigator Global Assessment; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; VAS: visual analogue scale