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Abrocitinib (atopic dermatitis) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Abrocitinib (atopische Dermatitis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 April 2022). Please note: This document was translated by an external translator and 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSA	body surface area
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EQ-5D	European Quality of Life-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
MOS	Medical Outcome Study
NRI	non-response imputation
NRS	numerical rating scale
PDE	phosphodiesterase
POEM	Patient-Oriented Eczema Measure
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SCORAD	Scoring Atopic Dermatitis
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
SPI	Sleep Problem Index
TCI	topical calcineurin inhibitor
TCS	topical corticosteroids
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 abrocitinib. 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 17 January 2022.

Research question

The aim of this report is to assess the added benefit of abrocitinib in comparison with the appropriate comparator therapy (ACT) of dupilumab for the treatment of moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy.

The research question presented in Table 2 was derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of abrocitinib[a]

Therapeutic indication	**ACT[b]**
Moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy[c]	Dupilumab (if applicable, in combination with TCS and/or TCI)

a. Abrocitinib may be used as monotherapy or with other drugs for topical use in atopic dermatitis.
b. Presented is the ACT specified by the G-BA.
c. As per approval, the therapeutic indication comprises patients who are candidates for systemic therapy. 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.

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

The company followed the G-BA's specification by identifying dupilumab as the ACT.

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 added benefit.

Study pool and study design

The study pool for the benefit assessment of abrocitinib in comparison with the ACT consists of the JADE DARE study. Said study is a randomized double-blind RCT comparing abrocitinib and dupilumab. The treatment duration was 26 weeks. The study enrolled adults with a diagnosis of moderate-to-severe atopic dermatitis for at least 6 months. In addition, patients had to either (A) have a history of inadequate response to ≥ 4 consecutive weeks of medicated

topical therapy for atopic dermatitis within 6 months prior to screening or (B) have required systemic therapy to control their disease within 1 year prior to study start.

A total of 362 patients were randomized to the abrocitinib arm and 365 patients to the dupilumab arm.

Patients in the intervention arm received 200 mg abrocitinib daily. The JADE DARE study did not allow dose modifications by tolerance and effectiveness as specified in the Summary of Product Characteristics (SPC). In the comparator arm, dupilumab was administered in accordance with the SPC. For the entire treatment duration, patients in both arms were to use emollients and, on active lesions, medicated topical therapies. Unless otherwise indicated, abrocitinib is hereinafter referred to as the intervention and dupilumab as the comparator therapy, despite the fact that both arms of the JADE DARE study involved medicated background therapy.

Primary outcomes of the study were improvement in the Peak Pruritus numerical rating scale (NRS) by ≥ 4 points at Week 2 and the Eczema Area and Severity Index (EASI) 90 at Week 4. Furthermore, the study surveyed patient-relevant outcomes on morbidity, health-related quality of life, and side effects.

Risk of bias and certainty of results

For the JADE DARE study, the risk of bias across outcomes is rated as low.

For each of the outcomes of all-cause mortality, pain (Skin Pain NRS), health status (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS]) as well as all outcomes of the side effects category, the risk of bias is likewise rated as low.

The risk of bias of results for each of the outcomes of remission (EASI 100), itching (Peak Pruritus NRS), sleep disturbance (Medical Outcome Study [MOS] Sleep Scale), patient-reported symptoms (Patient-Oriented Eczema Measure [POEM]), and health-related quality of life (Dermatology Life Quality Index [DLQI]) is deemed high due to the high and in some cases differential percentages of replaced values. However, the results are generally consistent with those from the additionally submitted sensitivity analyses. The certainty of results is therefore not downgraded despite the high risk of bias, and at most indications, e.g. of an added benefit, can be derived.

Results

Mortality

All-cause mortality

For the outcome of all-cause mortality, 2 deaths occurred in the abrocitinib arm and 0 deaths in the dupilumab arm. This results in no hint of an added benefit of abrocitinib in comparison with dupilumab; an added benefit is therefore not proven.

Morbidity

Symptoms – remission (EASI 100) and patient-reported symptoms (POEM 0–2)

For each of the outcomes of remission (EASI 100) and patient-reported symptoms (POEM 0-2), there is a statistically significant difference in favour or abrocitinib in comparison with dupilumab. This results in an indication of added benefit of abrocitinib in comparison with dupilumab for each of them.

Symptoms – itching (Peak Pruritus NRS), symptoms – sleep disturbances (MOS Sleep Scale Sleep Problem Index [SPI] I and SPI II), symptoms – pain (Skin Pain NRS), and health status (EQ-5D VAS)

No statistically significant difference between abrocitinib and dupilumab was found for any of the outcomes of itching (Peak Pruritus NRS 0–1), sleep disturbances (MOS Sleep Scale SPI I and SPI II, each improvement by ≥ 15 points), pain (Skin Pain NRS, mixed model for repeated measures [MMRM] analysis), and health status (EQ-5D VAS, MMRM analysis). This results in no hint of an added benefit of abrocitinib in comparison with dupilumab for any of them; an added benefit is therefore not proven.

Health-related quality of life

DLQI 0–1

In the DLQI 0–1, no statistically significant difference was found between abrocitinib and dupilumab. This results in no hint of an added benefit of abrocitinib in comparison with dupilumab; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs), discontinuation due to adverse events (AEs), infections, serious infections, and eye disorders (System Organ Class [SOC], AEs)

The present benefit assessment uses AEs which occurred in the SOC infections and infestations to analyse the outcome of infections, and it uses SAEs which occurred in said SOC to analyse the outcome of serious infections.

No statistically significant difference between abrocitinib and dupilumab was found for any of the outcomes of SAEs, discontinuation due to AEs, infections, serious infections, or eye disorders (SOC, AEs). This results in no hint of greater or lesser harm from abrocitinib in comparison with dupilumab for any of them; greater or lesser harm is therefore not proven.

Conjunctivitis (preferred term [PT], AEs)

For the outcome of conjunctivitis (PT, AEs), a statistically significant difference was found in favour of abrocitinib versus dupilumab. This results in an indication of lesser harm from abrocitinib in comparison with dupilumab.

Nervous system disorders (SOC, AEs), nausea (PT, AEs), and acne (PT, AEs)

For each of the outcomes of nervous system disorders (SOC, AEs), nausea (PT, AEs), and acne (PT, AEs), a statistically significant difference was found to the disadvantage of abrocitinib versus dupilumab. This results in an indication of greater harm from abrocitinib in comparison with dupilumab for each of them.

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

On the basis of the presented results, the probability and extent of added benefit of the drug abrocitinib in comparison with the ACT is assessed as follows:

Overall, both favourable and unfavourable effects were found for abrocitinib in comparison with dupilumab. For each of the outcomes of remission and patient-reported symptoms, an indication of considerable added benefit was found. No subgroup analyses are available for the outcome of remission. 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 with moderate-to-severe atopic dermatitis who are candidates for systemic therapy, there is an indication of considerable added benefit of abrocitinib in comparison with the ACT of dupilumab.

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

[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].

Table 3: 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 therapy[b]	Dupilumab (if applicable, in combination with TCS and/or TCI)	Indication of considerable 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 therapy. 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 approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of abrocitinib in comparison with the ACT of dupilumab in the treatment of moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy.

The research question presented in Table 4 was derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of abrocitinib[a]

Therapeutic indication	**ACT[b]**
Moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy[c]	Dupilumab (if applicable, in combination with TCS and/or TCI)

a. Abrocitinib may be used as monotherapy or with other drugs for topical use in atopic dermatitis.
b. Presented is the ACT specified by the G-BA.
c. As per approval, the therapeutic indication comprises patients who are candidates for systemic therapy. 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.

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

The company followed the G-BA's specification by identifying dupilumab as the ACT.

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 added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on abrocitinib (status: 16 November 2021)
- bibliographical literature search on abrocitinib (last search on 16 November 2021)
- search in trial registries / trial results databases for studies on abrocitinib (last search on 16 November 2021)
- search on the G-BA website for abrocitinib (last search on 16 November 2021)

To check the completeness of the study pool:

- search in trial registries for studies on abrocitinib (last search on 24 January 2022); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant studies.

2.3.1 Studies included

The study presented in the table below was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: abrocitinib versus dupilumab

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication (yes/no [reference])
B7451050 (JADE DARE[c])	No	Yes	No	Yes [3,4]	Yes [5,6]	No

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.
CSR: clinical study report; RCT: randomized controlled trial

The study pool for the benefit assessment of abrocitinib in comparison with the ACT coincides with the company's study pool and consists of the JADE DARE study. Abrocitinib can be used as monotherapy or with other drugs for topical use in atopic dermatitis. Unless otherwise indicated, abrocitinib is hereinafter referred to as the intervention and dupilumab as the comparator therapy, despite the fact that both arms of the JADE DARE study involved medicated background therapy (also see Section 2.3.2).

2.3.2 Study characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: abrocitinib versus dupilumab

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
JADE DARE	RCT, double-blind, parallel-group	Adults (≥ 18 years) with moderate-to-severe atopic dermatitis[b,c] who are candidates for systemic therapy[d]	Abrocitinib[e] (N = 362) Dupilumab[e] (N = 365)	Screening: 4 weeks Treatment: 26 weeks Follow-up observation: 4 weeks[f]	143[g] study centres in: Australia, Bulgaria, Canada, Chile, Germany, Finland, Hungary, Italy, Latvia, Poland, Slovakia, South Korea, Spain, Taiwan, United States 6/2020–7/2021	Primary: Improvement in Peak Pruritus NRS by ≥ 4 points at Week 2, EASI 90 at Week 4 Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account relevance for this benefit assessment. Secondary outcomes include information only on relevant available outcomes for this benefit assessment.
b. Chronic atopic dermatitis meeting the diagnostic criteria according to Hanifin and Rajka [7] with symptom onset at least 6 months prior to study start (before the study protocol's 2nd amendment dated 14 August 2020, at least 1 year).
c. For inclusion, patients had to meet the following criteria at baseline: body surface area affected ≥ 10%; IGA ≥ 3, EASI ≥ 16, and Peak Pruritus NRS ≥ 4.
d. For inclusion, patients had to meet one of the following criteria: (A) documented history (within 6 months prior to screening) of inadequate response to ≥ 4 consecutive weeks of medicated topical therapies for the treatment of AD or (B) systemic AD therapy received within 1 year prior to study start.
e. For the entire treatment duration, patients in both arms were to use emollients and, on areas with active lesions, medicated topical therapies (see Table 7).
f. Applies only to patients who did not participate in the double-blind extension study B7451015 with 100 mg or 200 mg abrocitinib.
g. Discrepancy between the dossier's Module 4 B and Module 5. Information obtained from the study report.

AD: atopic dermatitis; AE: adverse events; EASI: Eczema Area and Severity Index; IGA: Investigator Global Assessment; N: number of randomized patients; NRS: numerical rating scale; RCT: randomized controlled trial; TCS: topical corticosteroids

Table 7: Characteristics of the intervention – RCT, direct comparison: abrocitinib versus dupilumab

Study	Intervention	Comparison
JADE DARE	Abrocitinib 200 mg/day, orally, until Week 26 + Placebo s.c. on Day 1, followed by every 2 weeks until Week 24 (analogous to dupilumab)	Dupilumab 600 mg s.c. on Day 1, followed by 300 mg s.c. every 2 weeks until Week 24 + Placebo orally, once daily until Week 26 (analogous to abrocitinib)
	Background therapy[a] ▪ Emollients with or without active ingredients or other additives (e. g. hyaluronic acid, urea, ceramides, or filaggrin breakdown products), at least twice daily throughout the study period ▪ From Day 1: TCS once daily in areas with active lesions[b]: moderate-potency TCS; in areas with thin skin (e. g. face, neck, genital area) or in areas where continuous treatment with moderate-potency TCS is deemed potentially unsafe, low-potency TCS is to be used (or if necessary, TCI or PDE4 inhibitors). ▫ On controlled lesions (lesion-free or nearly lesion-free skin), TCS once daily for another 7 days, then discontinuation of TCS. ▫ In lesion recurrence, renewed treatment with moderate-potency or low-potency TCS. ▫ In case of documented intolerance after unsuccessful treatment switch, discontinuation of medicated background therapy. **Modification of study treatment** ▪ No dose modification allowed ▪ Interruption of oral medication for ≤ 28 days and ≤ 2 consecutive doses of the drug administered subcutaneously upon the physician's discretion. **Disallowed prior and concomitant treatment** ▪ Systemic JAK inhibitors ▪ IL4 or IL13 antagonists (e.g. Dupilumab, lebrikizumab, or tralokinumab) ▪ Biologics within 12 weeks or 5 half-lives (whichever is longer) prior to study start ▪ Live vaccines within 6 weeks prior to study start ▪ Oral immunosuppressant therapy[c] (e.g. with corticosteroids or ciclosporin) within 4 weeks or 5 half-lives (whichever is longer) prior to study start ▪ CYP2C9 and CYP2C19 inducers within 2 weeks plus 5 half-lives prior to study start; inhibitors within 1 week or 5 half-lives (whichever is longer) prior to study start ▪ Phototherapy, frequent solarium visits (> twice weekly), or herbal medicines with potential or proven effects in AD within 4 weeks prior to study start **Allowed concomitant treatment[a]** ▪ Rescue therapy[d]: high-potency TCS according to Table IV in Eichenfield et al. [8] for a maximum of 2 weeks, systemic corticosteroids for a maximum of 10 days, or other systemic therapies in accordance with Sidbury et al. [9], if deemed necessary by the investigator. ▪ Oral antihistamines	

a. Not directly provided by the sponsor or study centre.
b. Where such therapies had already been administered before study start, patients were allowed to continue them or de-escalate them according to a fixed strategy.
c. Systemic AD therapies were allowed in the context of what the company referred to as rescue therapy.
d. Allowed after Week 4 in patients who were deemed by the investigator to suffer from intolerable symptoms; study medication had to be interrupted for the duration of systemic rescue therapy. In case of topical rescue therapy, the study medication was continued.

AD: atopic dermatitis; CYP: cytochrome P450; IL: interleukin; JAK: Janus kinase; PDE: phosphodiesterase; RCT: randomized controlled trial; s.c.: subcutaneous; TCI: topical calcineurin inhibitors; TCS: topical corticosteroids

Study design

Study design, patient population and interventions

The JADE DARE study is a randomized double-blind RCT comparing abrocitinib and dupilumab. The treatment duration was 26 weeks. Afterwards, patients had the option of participating in a double-blind extension study [10] administering 100 mg or 200 mg abrocitinib.

The JADE DARE study enrolled adults who had been diagnosed with chronic atopic dermatitis for at least 6 months. Severity of disease was defined based on the following baseline criteria: ≥ 10% of body surface area (BSA) affected, Investigator Global Assessment (IGA) ≥ 3, EASI ≥ 16, and itching with a score of ≥ 4 on the Peak Pruritus NRS. For the present benefit assessment, the severity definition using the affected BSA, IGA, and EASI is deemed a sufficient approximation of moderate-to-severe atopic dermatitis.

To qualify for enrolment, patients additionally had to either have (A) had an inadequate response to ≥ 4 consecutive weeks of treatment with medicated topical therapy for atopic dermatitis within 6 months prior to screening or (B) required systemic therapies to control their disease within 1 year prior to study start. The available information does not include the applied definition of inadequate response.

Patients were randomized to the study arms using the stratification factor of severity of disease (IGA 3, IGA 4). A total of 362 patients were randomized to the abrocitinib arm and 365 patients to the dupilumab arm.

Patients in the intervention arm received 200 mg abrocitinib daily. This dosage corresponds to both the starting dose recommended for patients < 65 years of age and the maximum daily dose [11]. According to the SPC, the dose can be reduced or increased based on tolerance and efficacy. Further, patients on maintenance therapy should receive the lowest effective dose. However, the JADE DARE study did not allow dose modifications by tolerance and effectiveness as specified in the SPC. Interrupting abrocitinib therapy for up to 28 days was allowed if deemed indicated by the investigator. Regarding the timing of treatment modification, no clear criteria have been established, particularly not after treatment response. However, larger-scale dose modifications are not typically necessary yet within the JADE DARE study's relatively short treatment duration of 26 weeks. Therefore, the limitation of no dose modification options remains without consequence for the present assessment. Another limitation is that, in patients 65 years and older, the SPC specifies a starting dose of 100 mg. Hence, JADE DARE participants ≥ 65 years of age did not receive the starting dose approved for their age group. However, given that only 6% of participants in the intervention arm were ≥ 65 years of age (see Table 8), this deviation from the SPC likewise is of no consequence for the present assessment. In the comparator arm, dupilumab was administered in accordance with the SPC [12].

Primary outcomes of the study were improvement in Peak Pruritus NRS by ≥ 4 points at Week 2 and EASI 90 at Week 4. Furthermore, patient-relevant outcomes on morbidity, health-related quality of life, and side effects were surveyed.

Background therapy and rescue therapy

Throughout the treatment, patients were to apply emollients at least twice daily. In areas with active lesions, moderate-potency topical corticosteroids (TCS) were applied once daily, and in areas with intolerance or thin skin, low-potency TCS, topical calcineurin inhibitors (TCI), or phosphodiesterase (PDE) 4 inhibitors. Patients who had already received such therapies prior to study start were allowed to continue them. Background therapy with TCS, TCI, or any PDE4 inhibitors was de-escalated or reinitiated according to a defined regimen (see Table 7). Over 90% of patients received TCS, with moderate-potency TCS being less commonly used in the abrocitinib arm (66%) than in the comparator arm (76%). TCIs were used in about 20% of patients in both study arms, while PDE4 inhibitors were used very rarely (about 1% in both arms). The study documents do not show for how long patients were treated with abrocitinib monotherapy or dupilumab monotherapy – i.e. without medicated topical background therapy – over the course of the study.

Treatment escalation (which the company referred to as rescue therapy) with high-potency TCS, systemic corticosteroids, or other systemic therapies according to Sidbury et al. [9] was allowed after Week 4 if deemed necessary by the investigator. Few participants of the JADE DARE study received rescue therapy. In the abrocitinib arm and the dupilumab arm, 12 patients (3.3%) each received topical rescue therapy. According to the available documents, very-high-potency TCS were used as well. Systemic rescue therapy was administered to 4 patients (1.1%) in the abrocitinib arm and 2 patients (0.5%) in the dupilumab arm. The study medication had to be interrupted for the duration of systemic rescue therapy. In case of topical rescue therapy, the study medication was continued. Outcome recording was continued after rescue therapy.

Suitability of patients for systemic therapy

The "Systemic Therapy for Atopic Dermatitis" update to the German Atopic Dermatitis Guideline [13] includes the "establishing the indication for anti-inflammatory systemic therapy in adults" checklist. According to this guideline, patients are eligible for systemic therapy if they exhibit relevant objective severity (e.g. determined using the EASI score > 15 or affected BSA > 10%), relevant subjective burden (based on the DLQI measuring health-related quality of life [DLQI > 10], itching [> 6 on a VAS or NRS of 0 to 10], or relevant disturbance of night-time sleep due to itching/eczema), and lack of treatment response. The European guideline, in contrast, does not specify any strict subjective criteria for establishing the indication for systemic therapy [14,15].

The JADE DARE study's inclusion criteria ensure that participants exhibit the relevant objective severity and lack of treatment response because at baseline, patients had to have an EASI score ≥ 16 and either have shown inadequate response to topical therapies of atopic dermatitis or have already received systemic therapies. One half of patients had received

systemic therapy within 1 year prior to enrolment. Particularly systemic corticosteroids were used for this purpose. Approximately the other half of patients had received only topical therapy within 1 year prior to the first planned administration of the study medication, largely TCS of unknown potency (see Table 9). The study documents fail to show the percentage of patients who had an inadequate response to topical therapies. According to the inclusion criteria, however, it can be safely assumed that this applies at minimum to the about 50% of patients with exclusively topical prior therapy within 1 year prior to the first planned administration of the study drug; however, the JADE DARE study's definition of inadequate response remains unclear. Patients who received systemic therapy within the year prior to study start are also assumed to have exhibited an inadequate response to or be unsuitable for topical therapies.

To assess the relevant subjective burden, 3 criteria are listed in accordance with the above-mentioned checklist: DLQI > 10, itching > 6 on a VAS or NRS from 0 to 10, or relevant night-time sleep disturbance due to itching/eczema. Since no specific threshold is specified for night-time sleep disturbance, this criterion is not further taken into account below. IQWiG calculations based on means and standard deviations and assuming normal distribution in the study population show that over 65% of JADE DARE participants had a baseline DLQI ≥ 11. Over 70% of patients had a peak pruritus ≥ 7 at baseline (see Table 8). The patient population with a DLQI ≥ 11 and the population with peak pruritus ≥ 7 presumably do not fully overlap, and hence, at least 80% of the study population also meet the criterion of relevant subjective burden.

Overall, it is therefore assumed that continuous systemic therapy is an option for the JADE DARE study population.

Patient characteristics

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

Table 8: Characteristics of the study population as well as study/therapy discontinuation – RCT, direct comparison: abrocitinib versus dupilumab (multipage table)

Study **Characteristic** **Category**	**Abrocitinib** **N[a] = 362**	**Dupilumab** **N[a] = 365**
JADE DARE		
Age [years], mean (SD)	37 (15)	36 (13)
Age group, n (%)		
< 65 years	341 (94)	354 (97)
≥ 65 years	21 (6)	11 (3)
Sex [f/m], %	47/53	44/56
Ancestry, n (%)		
White	269 (74)	248 (68)
Black	25 (7)	26 (7)
Asian	62 (17)	83 (23)
Other	2 (1)[b]	3 (1)[b]
Not reported	4 (1)	5 (1)
Region, n (%)		
United States / Canada / Australia	177 (49)	195 (53)
Europe	150 (41)	132 (36)
Asia	17 (5)	19 (5)
Latin America	18 (5)	19 (5)
Disease duration: time from first diagnosis to randomization [months], mean (SD)	24.2 (14.1)	24.1 (14.1)
IGA, n (%)		
3 (moderate)	216 (60)	220 (60)
4 (severe)	146 (40)	145 (40)
EASI		
Mean (SD)	28.1 (11.5)	28.1 (11.9)
Median [Q1; Q3]	24.5 [19.4; 33.6]	24.5 [19.2; 33.5]
Affected BSA (%)		
Mean (SD)	42.5 (19.9)	42.6 (21.3)
Median [Q1; Q3]	39.0 [27.0; 55.0]	36.0 [26.0; 55.0]
Peak Pruritus NRS		
Mean (SD)	7.4 (1.6)	7.4 (1.6)
Median [Q1; Q3]	8.0 [7.0; 8.0]	7.0 [6.0; 9.0]
NRS 4-6, n (%)	83 (23)	105 (29)
NRS ≥ 7, n (%)	274 (76)	259 (71)
SCORAD		
Mean (SD)	67.8 (12.8)	66.8 (12.7)
Median [Q1; Q3]	66.4 [58.9; 76.8]	65.2 [58.0; 75.1]

Table 8: Characteristics of the study population as well as study/therapy discontinuation – RCT, direct comparison: abrocitinib versus dupilumab (multipage table)

Study Characteristic Category	Abrocitinib N[a] = 362	Dupilumab N[a] = 365
DLQI		
Mean (SD)	14.0 (6.8)	14.2 (6.3)
Median [Q1; Q3]	14.0 [9.0; 19.0]	14.0 [9.0; 19.0]
POEM		
Mean (SD)	20.4 (5.8)	20.9 (5.3)
Median [Q1; Q3]	21.0 [17.0; 25.0]	21.0 [18.0; 25.0]
Treatment discontinuation[c], n (%)	35 (9.7)	31 (8.5)
Study discontinuation, n (%)	ND	ND

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line, provided the deviation is relevant.
b. IQWiG calculations.
c. Most common reasons for treatment discontinuation in the intervention versus control arms (percentages based on randomized patients): withdrawal of consent (11 [3.0%] vs. 11 [3.0%] patients), AEs (including death) (12 [3.3%] vs. 9 [2.5%] patients); the dossier's Module 5 additionally includes data on study discontinuation due to AEs, probably including death (12 [3.3%] vs. 9 [2.5%] patient) as well as on treatment discontinuation due to AEs with simultaneous study continuation (0 [0%] vs. 1 [0.3%] patients). Hence, the expected figures for treatment discontinuation due to AEs is 12 [3.3%] vs. 10 [2.7%].

AE: adverse event; BSA: body surface area; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; f: female; IGA: Investigator Global Assessment; m: male; max.: maximum; min.: minimum; n: number of patients in the category; N: number of randomized patients; NRS: numerical rating scale; POEM: Patient-Oriented Eczema Measure; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SCORAD: Scoring Atopic Dermatitis; SD: standard deviation

Patient characteristics are sufficiently balanced between the 2 treatment groups.

In the 2 study arms, the mean patient age was 37 and 36 years, respectively, and the majority of patients were white. Slightly less than half of patients were female. The mean time since diagnosis of atopic dermatitis was about 24 years.

According to the EASI and Scoring Atopic Dermatitis (SCORAD) severity categorizations, most of the included patients suffered from severe disease [16]. According to the IGA severity classification, 60% of both treatment groups had moderate severity of disease. The majority of patients in both treatment groups rated itching at baseline as ≥ 7 on the Peak Pruritus NRS.

In both treatment groups, fewer than 10% of patients discontinued therapy. No data are available on treatment discontinuation.

Table 9 presents the prior therapies of patients in the JADE DARE study.

Table 9: Characteristics of the study population (prior therapy) – RCT, direct comparison: abrocitinib versus dupilumab

Study Characteristic Category	Abrocitinib N = 362	Dupilumab N = 365
JADE DARE		
Any prior AD therapy	360 (99.4)[a]	365 (100)
Exclusively topical prior therapy[b], n (%)	188 (51.9)	189 (51.8)
Low to moderate-potency TCS (classes III–VII[c])	25 (6.9)	17 (4.7)
High-potency TCS (classes I–II[c])	20 (5.5)	22 (6.0)
TCS of unknown potency	137 (37.8)	148 (40.5)
Crisaborol	9 (2.5)	3 (0.8)
TCI	60 (16.6)	50 (13.7)
Topical JAK inhibitors	2 (0.6)	1 (0.3)
Systemic prior therapy[d]	172 (47.5)	176 (48.2)
Nonbiologic agents	164 (45.3)	168 (46.0)
Corticosteroids	139 (38.4)	136 (37.3)
Ciclosporin	39 (10.8)	50 (13.7)
Other nonbiologic agents	30 (8.3)	37 (10.1)
Biologic agents	8 (2.2)	8 (2.2)
Medical procedures, n (%)		
PUVA	4 (1.1)	1 (0.3)
Phototherapy	8 (2.2)	10 (2.7)
UV light therapy	25 (6.9)	22 (6.0)

a. IQWiG calculations.
b. Topical prior therapies within 1 year prior to the first planned administration of the study medication.
c. Classified in accordance with Eichenfield et al. [8]
d. Any systemic therapy in the patients' medical history prior to the first planned administration of the study medication.

AD: atopic dermatitis; JAK: Janus kinase; n: number of patients in the category; N: number of randomized patients; PUVA: Psoralen UVA treatment; RCT: randomized controlled trial; TCI: topical calcineurin inhibitors; TCS: topical corticosteroids; UV: ultraviolet

The JADE DARE treatment groups were balanced with regard to the administered prior therapies; see above for a further evaluation of the provided data.

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: abrocitinib versus dupilumab

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of additional aspects	Risk of bias at study level
			Patients	Treatment providers			
JADE DARE	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

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

Transferability of the study results to the German health care context

The company reports that the JADE DARE study was carried out primarily in Western industrialized countries, including in Germany, on patients of predominantly white ancestry. In addition, the company refers to the subgroup analyses by ancestry and region provided in Module 4 A, according to which there are no conclusion-relevant effect modifications; therefore, JADE DARE results can be deemed transferable to the Germany healthcare context.

The company has provided no further information on the transferability of study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be taken into account in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - symptoms – remission (surveyed using EASI 100)
  - symptoms – itching (surveyed using Peak Pruritus NRS)
  - symptoms – sleep disturbances (surveyed using MOS Sleep Scale)
  - symptoms – pain (surveyed using Skin Pain NRS)
  - patient-reported symptoms (surveyed using POEM)
  - health status (recorded with the EQ-5D VAS)
- Health-related quality of life

- health-related quality of life (recorded with the DLQI)

- Side effects
  - SAEs
  - discontinuation due to adverse events (AEs)
  - infections (SOC infections and infestations, AEs)
  - serious infections (SOC infections and infestations, SAEs)
  - conjunctivitis (PT, AEs)
  - eye disorders (SOC, AEs)
  - further specific AEs, if any

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

Table 11 shows the outcomes for which data were available in the included study.

Table 11: Matrix of outcomes – RCT, direct comparison: abrocitinib versus dupilumab

Study	Outcomes														
	All-cause mortality	Symptoms – remission (EASI 100[a])	Symptoms – itching (Peak Pruritus NRS)	Symptoms – sleep disorders (MOS Sleep Scale)	Symptoms – pain (Skin Pain NRS)	Patient-reported symptoms (POEM)	Health status (EQ-5D VAS)	Health-related quality of life (DLQI)	SAEs[b]	Discontinuation due to AEs[b]	Infections (SOC, AEs)[c]	Serious infections (SOC, SAEs)[c]	Conjunctivitis (PT, AEs)	Eye disorders (SOC, AEs)	Further specific AEs[d]
JADE DARE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Score improvement by 100% from baseline.
b. Includes events related to the underlying disorder (PT atopic dermatitis); in the dossier's Appendix 4-G, AE and SAE events are each presented excluding progression events. However, no information is available on the events which were disregarded.
c. All AEs from the MedDRA SOC infections and infestations were used to record infections, and all SAEs were used to record serious infections.
d. The following (MedDRA-coded) events were considered: nervous system disorders (SOC, AEs), nausea (PT, AEs), and acne (PT, AEs).

AE: adverse event; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; MedDRA: Medical Dictionary for Regulatory Activities; MOS: Medical Outcome Study; NRS: numerical rating scale; POEM: Patient-Oriented Eczema Measure; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

Notes regarding outcomes

Unclear predefinition status of some analyses

Knowing whether the respective analysis is a predefined one is important, particularly for using responder analyses employing a minimal important difference (MID) in accordance with IQWiG General Methods [1]. For some of the analyses, the available documents do not provide this information (see below). Some analyses are listed neither in the study protocol nor in version 1 of the statistical analysis plan (SAP) dated 17 January 2020, but only as supplementary analyses in SAP version 2 dated 21 July 2021. The last visit of the last patient was on 13 July 2021 and hence before the date of SAP version 2. In addition, no date was provided as to when the database was closed. Hence, it is unclear whether these analyses were predefined, and for the purposes of this benefit assessment, the analyses are therefore assumed to have been specified post hoc.

Symptoms – EASI

EASI is an instrument used for an objective survey of the severity of atopic dermatitis [17]. In this instrument, the physician rates the symptoms of erythema, oedema / papule development, abrasions, and skin lichenification using a symptom score of between 0 (no symptoms) and 3 (severe symptoms) and additionally estimates the percentage of the affected BSA in percent of the total BSA. With the various values being weighted differently, a total score ranging from 0 to 72 was calculated. Higher values indicate more severe disease.

EASI 100 at Week 26 was used for the present assessment. EASI 100 means complete remission of external signs of dermatitis (i.e. reduction to a score of 0). Rather than presenting the EASI 100 results in Module 4 A, the company used EASI 75 and EASI 90 (75% or 90% reduction of the EASI baseline score [response]) at Week 26 to derive added benefit. The results on these analyses are presented as supplementary information in Appendix B of the full dossier assessment.

Symptoms – SCORAD

SCORAD is an established instrument for assessing the severity of atopic dermatitis [18-20]. In this tool, a physician rates the spread of skin changes and assesses their intensity regarding 6 symptoms of atopic dermatitis on a scale of 0 (no symptoms) to 3 (severe symptoms). In addition, patients rate the average severity of the 2 symptoms of sleeplessness and itching for the previous 3 days or nights, each on a VAS ranging from 0 (no symptoms) to 10 (most severe symptoms). With the various components being weighted differently, a total score ranging from 0 to 103 is calculated. Higher values indicate more severe disease.

Due to the instrument's design, assessing the clinical relevance of changes in the SCORAD total score is difficult. Therefore, it is necessary to analyse SCORAD 100 (i.e. improvement by 100% from baseline). The JADE DARE study did not provide for an analysis of SCORAD 100, and the company has not submitted any post hoc analysis of SCORAD 100. For the symptoms of sleeplessness and itching included in the SCORAD total score, the JADE DARE study also provided separate analyses (see below).

SCORAD 75 and SCORAD 90 (75% or 90% reduction in baseline SCORAD score [response]) at Week 26 are presented as supplementary information in Appendix B of the full dossier assessment.

Symptoms – itching (Peak Pruritus NRS and SCORAD VAS)

The company's Module 4 A presents itching results from the Peak Pruritus NRS and SCORAD VAS for itching, each at Week 26.

Peak Pruritus NRS is a self-rating instrument to determine maximum itching within the previous 24 hours [21]. Values are recorded using a numerical scale from 0 (no itching) to 10 (worst imaginable itching). JADE DARE surveyed itching daily with the Peak Pruritus NRS

entered an electronic patient diary. The SCORAD VAS for itching asks about itching within the past 3 days or nights.

The present benefit assessment uses the operationalization of Peak Pruritus NRS 0–1 at Week 26, representing very low to nonexistent symptom burden. This operationalization better reflects the absence of itching as a desired and – under systemic continuous abrocitinib or dupilumab therapy – generally achievable treatment goal than does the company's response criterion of improvement by ≥ 4 points at Week 26.

An analysis depicting (almost complete) absence of itching is available for Peak Pruritus NRS, but not for the SCORAD VAS for itching. Therefore, SCORAD VAS for itching was disregarded in the present benefit assessment. Furthermore, the analysis of ≥ 2 points improvement on SCORAD VAS at Week 26 was specified post hoc, with the response criterion corresponding to > 15% of the scale range. According to the IQWiG General Methods [1], however, analyses specified post hoc are to be taken into account only if the response criterion equalled exactly 15% of the scale range.

Symptoms – sleep disorders (MOS Sleep Scale and SCORAD VAS)

In Module 4 A, the company presents results on sleep disturbances from the survey using the MOS Sleep Scale and SCORAD VAS for sleep disturbances.

The MOS Sleep Scale is an instrument with a total of 12 items surveying sleep quality. The JADE DARE study used the version surveying sleep quality within the previous 4 weeks. The company presented analyses on the Sleep Problem Indices (SPI) I and II. The SPI I is calculated based on 6 items, and the SPI II, on an additional 3 items. From the questionnaire items, 5 further scales can be calculated, but most of the associated items are already included in the 2 indices [22]. The items and the scales each range from 0 to 100 [23], with higher values indicating greater problems sleeping. In Module 4 A, the company presents responder analyses of improvement in SPI I and II by > 15 points.

The SCORAD VAS on sleeplessness surveys sleeplessness within the prior 3 days or nights. From the SCORAD VAS on sleeplessness, the company derived added benefit based on analyses of improvement by ≥ 2 points.

The present benefit assessment used the analyses of the MOS Sleep Scale. The analyses of the SCORAD VAS on sleep disturbance were disregarded since the MOS Sleep Scale questionnaire depicts sleep disorders more comprehensively than does a single question (SCORAD VAS). Furthermore, the analysis of improvement by ≥ 2 points presented by the company for SCORAD VAS is irrelevant because the response criterion corresponds to > 15% of the scale range and the analysis is assumed to have been specified post hoc (see above). According to the IQWiG General Methods [1], however, analyses specified post hoc are to be taken into account only if the response criterion equalled exactly 15% of the scale range.

Symptoms – pain (Skin Pain NRS)

The Skin Pain NRS is a self-rating instrument for surveying maximum pain within the last 24 hours [24]. Data are recorded using a numerical scale from 0 (no pain) to 10 (worst pain imaginable).

The analyses submitted by the company using an MMRM are used for the present benefit assessment. The analysis of improvement by ≥ 4 points is disregarded because it is assumed to have been specified post hoc (see above) and the response criterion corresponds to > 15% of the scale range. According to the IQWiG General Methods [1], however, analyses specified post hoc are to be taken into account only if the response criterion equalled exactly 15% of the scale range.

Patient-reported symptoms (POEM)

POEM is an instrument for surveying symptoms in patients with atopic dermatitis [20,25,26]. The questionnaire surveys the frequency of occurrence of 7 different symptoms of atopic dermatitis (itching, sleep disturbances, skin bleeding, skin weeping or oozing, cracked skin, flaking skin, dry/rough skin) within the previous week. Frequency is surveyed with a Likert scale (0 [no day], 1 [1 to 2 days], 2 [3 to 4 days], 3 [5 to 6 days], 4 [every day]). A total score is calculated, ranging from 0 to 28. Higher values indicate more frequent symptoms.

The present benefit assessment uses the operationalization of POEM 0–2 at Week 26, representing very low to nonexistent symptom burden. The company additionally used the analysis of improvement by ≥ 5 points.

Health status (EQ-5D VAS)

In Module 4 A, the company reportedly presented results on patients who achieved an improvement (reduction) in EQ-5D VAS by ≥ 15 points from baseline at Week 26. Based on the information the company provided in Module 4 A, however, it is safe to assume that the presented analysis represents in fact a deterioration of health status since lower values indicate poorer health status. Due to the expected course of disease in the present therapeutic indication, an analysis of health status improvement is primarily relevant for the present benefit assessment. Therefore, this benefit assessment uses the analyses presented by the company with the MMRM on EQ-5D VAS.

Side effects

For AEs and SAEs, the company presents analyses excluding events which it deems to be symptoms or deteriorations of symptoms (progression) of the underlying disorder. These analyses are being disregarded in the present benefit assessment because no information is available on which events were excluded. Technically, the present assessment would benefit from analyses excluding events occurring in the PT of atopic dermatitis. However, given that the available data for the PT of atopic dermatitis showed only isolated events which were rated

as SAEs or led to discontinuation, the available analyses of SAEs and discontinuation due to AEs are sufficiently interpretable and suitable for the benefit assessment.

Notes regarding statistical methods and effect measures

For the outcomes of patient-reported symptoms (POEM 0–2), sleep disturbances (MOS Sleep Scale), and health-related quality of life (DLQI 0–1), the company's responder analyses at Week 26 were used, in which values after treatment discontinuation or after rescue therapy as well as missing values were replaced using non-response imputation (NRI). The company determined relative risk (including confidence interval and statistical test) by means of the Cochran–Mantel–-Haenszel method, taking into account stratification by baseline disease severity (IGA = 3 versus IGA = 4).

An analysis where only missing values are replaced would be preferable to the one supplied by the company. For instance, outcomes continued to be surveyed after rescue therapy (see Section 2.3.2). In patients discontinuing treatment, data were surveyed immediately after discontinuation and after 4 weeks.

In addition, replacement procedures such as NRI present the general problem that the enlargement of sample size tends to increase the precision of the resulting effect estimate despite the fact that the replacement of missing values actually tends to increase uncertainty. This increased uncertainty can be taken into account by estimating the missing values using Higgins' modified estimation of variance [27].

A separate calculation was therefore carried out for the above-mentioned outcomes as well as for operationalizations presented as supplementary information (see Appendix B of the full dossier assessment). The submitted documents were used to determine the number of responders from among patients with an available survey after rescue therapy; doing so was impossible for patients with treatment discontinuation because the necessary information is not available. That is, only values after treatment discontinuation and missing values were replaced using NRI. In addition, the stated variance correction was applied. Due to the IQWiG analysis being qualitatively and quantitatively consistent with the company's above-described analysis, the company's results were used for the benefit assessment.

For the outcomes of remission (EASI 100) and itching (Peak Pruritus NRS 0–1), IQWiG performed analyses at Week 26 on the basis of data from the study documents. In this case, values after treatment discontinuation or after rescue therapy as well as missing values were likewise replaced using NRI. However, the analysis applied the described variance correction.

For the outcomes of pain (Skin Pain NRS) and health status (EQ-5D VAS), the company's analyses with MMRM (with the factors of treatment and visit, the interaction term visit x treatment as well as the respective baseline score and baseline disease severity as covariates) were used. This analysis likewise disregarded results surveyed after treatment

discontinuation or after rescue therapy. The results used in each case represent the difference between treatment groups in changes from baseline to Week 26.

For the outcomes of the side effects category, the presented relative risks (including confidence interval and statistical test) were likewise used. In this case, the company carried out unstratified analyses.

Notes on sensitivity analyses

Section 4.2.5.4 of the dossier's Module 4 A contains information on the methods used for sensitivity analyses and on the factors for which sensitivity analyses were carried out to check the robustness of results.

For each of the outcomes of the morbidity and health-related quality of life categories which are relevant for this benefit assessment, the company submitted both the responder analyses at Week 26, which it refers to as "main analysis" and where values surveyed after treatment discontinuation or after rescue therapy as well as missing values are replaced by NRI, as well as 3 further responder analyses:

- Analysis of observed cases at Week 26, where values observed after rescue therapy were deemed missing values; the handling of any values observed after treatment discontinuation was not described.
- Analysis at Week 26, with values observed after rescue therapy being included and non-response imputation being applied in patients after treatment discontinuation
- Analysis at Week 26 using multiple imputation, including values observed after rescue therapy, but not those after treatment discontinuation

Furthermore, the company submitted MMRM analyses of change from baseline for all survey time points. These are the analyses used in the present benefit assessment for the outcomes of pain (Skin Pain NRS) and health status (EQ-5D VAS) (see above).

For some instruments, the company submitted responder analyses using various response criteria in addition to the sensitivity analyses described in Module 4 A Section 4.2.5.4. For some instruments and response criteria, the company also presented further analyses such as responder analyses for various survey points over the course of the study or an analysis of days with response.

2.4.2 Risk of bias

Table 12 shows the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: abrocitinib versus dupilumab

Study		Outcomes														
	Study level	All-cause mortality	Symptoms – remission (EASI 100[a])	Symptoms – itching (Peak Pruritus NRS)	Symptoms – sleep disorders (MOS Sleep Scale)	Symptoms – pain (Skin Pain NRS)	Patient-reported symptoms (POEM)	Health status (EQ-5D VAS)	Health-related quality of life (DLQI)	SAEs[b]	Discontinuation due to AEs[b]	Infections (SOC, AEs)[c]	Serious infections (SOC, SAEs)[c]	Conjunctivitis (PT, AEs)	Eye disorders (SOC, AEs)	Further specific AEs[d]
JADE DARE	L	L	H[e]	H[e]	H[e]	L	H[e]	L	H[e]	L	L	L	L	L	L	L

a. Score improvement by 100% from baseline.
b. Includes events of the underlying disorder; in the dossier's Appendix 4-G, the results on AEs and SAEs are each presented without progression events. However, no information is available on the events which were disregarded.
c. All AEs from the MedDRA SOC infections and infestations were used to record infections, and all SAEs were used to record serious infections.
d. The following (MedDRA-coded) events were considered: nervous system disorders (SOC, AEs), nausea (PT, AEs), and acne (PT, AEs).
e. High or differing percentages of NRI-replaced values (see Table 13); despite the high risk of bias, the certainty of results is deemed to be high (see body of text).

AE: adverse event; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; MOS: Medical Outcome Study; NRI: non-response imputation; NRS: numerical rating scale; POEM: Patient-Oriented Eczema Measure; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of results is deemed low for each of the outcomes of all-cause mortality, pain (Skin Pain NRS), health status (EQ-5D VAS) as well as all outcomes of the side effects category.

The risk of bias of results for the outcomes of remission (EASI 100), itching (Peak Pruritus NRS), sleep disturbances (MOS Sleep Scale), patient-reported symptoms (POEM), and health-related quality of life (DLQI) is deemed high due to the high and differential percentages of replaced values in some cases (see Table 13). However, the results are generally consistent with those from the additionally submitted sensitivity analyses. The certainty of results is therefore not downgraded despite the high risk of bias, and at most indications, e.g. of an added benefit, can be derived.

Table 13: Overview of replaced values in responder analyses in 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** **N = 362**	**Dupilumab** **N = 365**
Remission (EASI 100)		
N* (%[a]) in analysis (NRI[b])	362 (100)	365 (100)
Replaced values (NRI), n (%[c])	61 (16.9)	41 (11.2)
Itching (Peak Pruritus NRS 0–1)		
N* (%[a]) in analysis (NRI[b])	362 (100)	365 (100)
Replaced values (NRI), n (%[c])	49 (13.5)	37 (10.1)
Sleep disturbances (MOS Sleep Scale SPI I, improvement by ≥ 15 points[d])		
N* (%[a]) in analysis (NRI[b])[e]	362 (100)	363 (99.5)
Replaced values (NRI), n (%[c])	61 (16.9)	43 (11.8)
Sleep disturbances (MOS Sleep Scale SPI II, improvement by ≥ 15 points[d])		
N* (%[a]) in analysis (NRI[b])[e]	362 (100)	364 (99.7)
Replaced values (NRI), n (%[c])	61 (16.9)	43 (11.8)
Patient-reported symptoms (POEM 0–2)		
N* (%[a]) in analysis (NRI[b])[f]	358 (98.9)	363 (99.5)
Replaced values (NRI), n (%[c])	59 (16.5)	43 (11.8)
Health-related quality of life (DLQI 0–1)		
N* (%[a]) in analysis (NRI[b])[g]	358 (98.9)	361 (98.9)
Replaced values (NRI), n (%[c])	58 (16.2)	40 (11.1)

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 ≥ 15 points from baseline, at a scale range of 0 to 100. Lower (decreasing) values indicate an improvement of symptoms.
e. The analysis included patients with a baseline score ≥ 15 points.
f. The analysis included patients with a baseline score ≥ 3 points.
g. The analysis included patients with a baseline score ≥ 2 points.

DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; MOS: Medical Outcome Study; N: number of analysed patients; N*: number of analysed patients; n: number of replaced values; NRI: non-response imputation; NRS: numerical rating scale; POEM: Patient-Oriented Eczema Measure; SPI: Sleep Problem Index

2.4.3 Results

Table 14 and Table 15 summarize the results on the comparison of abrocitinib with dupilumab in adults with moderate to severe atopic dermatitis who are candidates for systemic therapy. Where necessary, IQWiG calculations are provided in addition to the data from the company's dossier.

Tables on common AEs, SAEs, and discontinuation due to AEs are presented in Appendix C of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: abrocitinib versus dupilumab (multipage table)

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					
Mortality					
All-cause mortality[b]	362	2 (0.6[c])	365	0 (0)	–
Morbidity[d, e]					
Symptoms					
Remission (EASI 100)	362	79 (21.8[c])	365	50 (13.7[c])	1.59 [1.13; 2.25]; 0.009[f]
Itching (Peak Pruritus NRS 0–1)	362	139 (38.4[c])	365	114 (31.2[c])	1.23 [0.99; 1.52]; 0.058[f]
Sleep disorders (MOS Sleep Scale)					
SPI I (improvement by ≥ 15 points[g])	362	131 (36.2)	363	117 (32.2)	1.12 [0.92; 1.37]; 0.264
SPI II (improvement by ≥ 15 points[g])	362	139 (38.4)	364	140 (38.5)	1.00 [0.83; 1.20]; 0.972
Patient-reported symptoms (POEM 0–2)	358	106 (29.6)	363	69 (19.0)	1.56 [1.19; 2.03]; 0.001
Health-related quality of life[d,e]					
DLQI 0–1	358	137 (38.3)	361	114 (31.6)	1.21 [0.99; 1.48]; 0.060
Side effects[d]					
AEs[h] (presented as supplementary information)	362	268 (74.0)	365	239 (65.5)	–
SAEs[h]	362	6 (1.7)	365	6 (1.6)	1.01 [0.33; 3.10]; 0.989
Discontinuation due to AEs[h,i]	362	9 (2.5)	365	9 (2.5)	1.01 [0.40; 2.51]; 0.986
Infections (SOC, AEs)[j]	362	110 (30.4)	365	109 (29.9)	1.02 [0.82; 1.27]; 0.916[k]
Serious infections (SOC, SAEs)[j]	362	3 (0.8)	365	0 (0)	–
Conjunctivitis (PT, AEs)	362	8 (2.2)	365	35 (9.6)	0.23 [0.11; 0.49]; < 0.001
Eye disorders (SOC, AEs)	362	17 (4.7)	365	28 (7.7)	0.61 [0.34; 1.10]; 0.103[k]
Nervous system disorders (SOC, AEs)	362	70 (19.3)	365	33 (9.0)	2.14 [1.45; 3.15]; < 0.001[k]
Nausea (PT, AEs)	362	70 (19.3)	365	8 (2.2)	8.82 [4.31; 18.07]; < 0.001
Acne (PT, AEs)	362	46 (12.7)	365	10 (2.7)	4.64 [2.38; 9.05]; < 0.001

Table 14: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: abrocitinib versus dupilumab (multipage table)

Study	Abrocitinib		Dupilumab		Abrocitinib vs. dupilumab
Outcome category Outcome	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]

a. Unless otherwise indicated, outcomes of the side effects and health-related quality of life categories: Cochran–Mantel–Haenszel method, stratified by disease severity at baseline (IGA = 3 vs. IGA = 4); outcomes of the side effects category: asymptotic, unstratified.
b. Deaths were recorded under AEs.
c. IQWiG calculation.
d. Morbidity and health-related quality of life: analysis at Week 26; side effects: analysis at Week 26 as well as plus 28 days in patients with follow-up phase.
e. Values after treatment discontinuation or rescue therapy as well as missing values were likewise replaced using non-response imputation.
f. IQWiG calculation of RR, 95% CI and p-value; asymptotic, with variance correction in accordance with data-set re-sizing approach [27].
g. Improvement is defined as a decrease by ≥ 15 points from baseline, at a scale range of 0 to 100. Lower (decreasing) values indicate an improvement of symptoms.
h. Includes events of the underlying disorder (PT atopic dermatitis); in the dossier's Appendix 4-G, the results on AEs and SAEs are each presented without progression events. However, no information is available on which events were disregarded (see Section 2.4.1).
i. The dossier's Module 5 presents data on discontinuation due to AEs, on study discontinuation due to AEs, likely including death, (12 [3.3%] vs. 9 [2.5%] patients) as well as on treatment discontinuation due to AEs with continued study participation (0 [0%] vs. 1 [0.3%] patients). Hence, the expected figures for treatment discontinuation due to AEs is 12 [3.3%] vs. 10 [2.7%].
j. To survey infections, all AEs of the MedDRA SOC infections and infestations were used, and to survey serious infections, all SAEs.
k. IQWiG calculation of RR, 95% CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [28]).

AE: adverse event; CI: confidence interval; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; IGA: Investigator Global Assessment; MedDRA: Medical Dictionary for Regulatory Activities; MOS: Medical Outcome Study; n: number of patients with (at least 1) event; N: number of analysed patients; NRS: numerical rating scale; POEM: Patient-Oriented Eczema Measure; PT: preferred term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: system organ class; SPI: Sleep Problem Index; VAS: visual analogue scale

Table 15: Results (morbidity, continuous) – RCT, direct comparison: abrocitinib versus dupilumab

Study Outcome category Outcome	Abrocitinib			Dupilumab			Abrocitinib vs. dupilumab
	N[a]	Values at baseline mean (SD)	Change Week 26 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change Week 26 mean[b] (SE)	MD [95% CI]; p-value[b]
JADE DARE							
Morbidity							
Symptoms							
Pain (Skin Pain NRS[c])	362	6.5 (2.4)	-4.51 (0.12)	365	6.3 (2.3)	-4.32 (0.12)	-0.19 [-0.53; 0.14]; 0.266
Health status (EQ-5D VAS[d])	362	68.4 (19.5)	13.48 (0.76)	364	67.7 (18.3)	14.30 (0.75)	-0.82 [-2.91; 1.28]; 0.445

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may be based on different patient numbers.
b. Mean and SE (per treatment group at Week 26) as well as MD, 95% CI and p-value (between-group comparison): MMRM with the factors of treatment and visit, the interaction term visit x treatment as well as the respective baseline score and baseline disease severity as covariates; effect represents the difference between treatment groups in changes from baseline at Week 26; values after treatment discontinuation and after rescue therapy were deemed missing values.
c. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention (scale range of 0 to 10).
d. Higher (increasing) values indicate improved symptoms; positive effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 100).

CI: confidence interval; MD: mean difference; MMRM: mixed effect model repeated measurement; N: number of analysed patients; NRS: numerical rating scale; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale

Based on the available information, at most indications, e.g. of an added benefit, can be determined for all outcomes (see Section 2.4.2).

Mortality

All-cause mortality

For the outcome of all-cause mortality, 2 deaths occurred in the abrocitinib arm and 0 deaths in the dupilumab arm. This results in no hint of an added benefit of abrocitinib in comparison with dupilumab; an added benefit is therefore not proven.

Morbidity

Symptoms – remission (EASI 100) and patient-reported symptoms (POEM 0–2)

For each of the outcomes of remission (EASI 100) and patient-reported symptoms (POEM 0-2), there is a statistically significant difference in favour or abrocitinib in comparison with dupilumab. This results in an indication of added benefit of abrocitinib in comparison with dupilumab for each of them.

Symptoms – itching (Peak Pruritus NRS), symptoms –sleep disturbances (MOS Sleep Scale I and SPI II), symptoms – pain (Skin Pain NRS), and health status (EQ-5D VAS)

No statistically significant difference between abrocitinib and dupilumab was found for any of the outcomes of itching (Peak Pruritus NRS 0–1), sleep disturbances (MOS Sleep Scale SPI I and SPI II, each improvement by ≥ 15 points), pain (Skin Pain NRS, MMRM analysis), and health status (EQ-5D VAS, MMRM analysis). This results in no hint of an added benefit of abrocitinib in comparison with dupilumab for any of them; an added benefit is therefore not proven.

Health-related quality of life

DLQI 0–1

In the DLQI 0–1, no statistically significant difference was found between abrocitinib and dupilumab. This results in no hint of an added benefit of abrocitinib in comparison with dupilumab; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs, infections, serious infections, and eye disorders (SOC, AEs)

The present benefit assessment uses AEs which occurred in the SOC infections and infestations to analyse the outcome of infections, and it uses SAEs which occurred in said SOC to analyse the outcome of serious infections.

No statistically significant difference between abrocitinib and dupilumab was found for any of the outcomes of SAEs, discontinuation due to AEs, infections, serious infections, or eye disorders (SOC, AEs). This results in no hint of greater or lesser harm from abrocitinib in comparison with dupilumab for any of them; greater or lesser harm is therefore not proven.

Conjunctivitis (PT, AEs)

For the outcome of conjunctivitis (PT, AEs), a statistically significant difference was found in favour of abrocitinib versus dupilumab. This results in an indication of lesser harm from abrocitinib in comparison with dupilumab.

Nervous system disorders (SOC, AEs), nausea (PT, AEs), and acne (PT, AEs)

For each of the outcomes of nervous system disorders (SOC, AEs), nausea (PT, AEs), and acne (PT, AEs), a statistically significant difference was found to the disadvantage of abrocitinib versus dupilumab. This results in an indication of greater harm from abrocitinib in comparison with dupilumab for each of them.

2.4.4 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 (IGA 3 vs. IGA 4)

No subgroup analyses are available for the analyses of the outcomes of remission (EASI 100), itching (Peak Pruritus NRS 0–1), pain (Skin Pain NRS), and health status (EQ-5D VAS).

The company submitted subgroup analyses of AEs by SOC and PT which occurred in at least 10% of patients or at least 10 patients and 1% of patients in at least 1 study arm. However, PTs (and SOCs) below the cutoff are not presented therein, nor are these PTs included in the SOCs. As a result, the subgroup analyses on SOCs presented by the company do not include all events which occurred. Hence, the subgroup analyses on the specific AEs of infections, eye disorders (SOC, AEs) as well as nervous system disorders (SOC, AEs) are unusable.

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. Subgroup results where the extent did not differ between subgroups are not presented.

In accordance with the described methods, no relevant effect modification by sex, age, or disease severity was identified for the outcomes for which subgroup analyses are available.

2.5 Probability and extent of added benefit

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

The approach for deriving an overall conclusion on 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.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 16).

Determination of the outcome category for symptom outcomes

For the symptoms outcomes below, it cannot be directly inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms – Remission (EASI 100)

The allocation of the outcome of remission (EASI 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 EASI value of 24.5, above 21, in both treatment groups. The median EASI values are therefore in the high-severity range [29]. Hence, the outcome of remission (EASI 100) is assigned to the outcome category of serious/severe symptoms / late complications.

Symptoms – patient-reported symptoms (POEM 0–2)

POEM is a questionnaire for subjectively recording the frequency of the symptoms of atopic dermatitis. On the basis of the baseline scores for itching and EASI (surveying some of the same symptoms as POEM), the symptoms are largely to be deemed serious/severe (see Table 8). Therefore, the outcome of patient-reported symptoms (POEM 0–2) is assigned to the outcome category of serious/severe symptoms / late complications.

Table 16: 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 [1.13; 2.25] RR: 0.63 [0.44; 0.88][c] p = 0.009 Probability: indication	Outcome category: serious/severe symptoms / late complications $0.75 \leq CI_u < 0.90$ Added benefit; extent: considerable
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
Sleep disorders (MOS Sleep Scale)		
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)	-4.51 vs. -4.32 MD: -0.19 [-0.53; 0.14] p = 0.266	Lesser/added benefit not proven
Patient-reported symptoms (POEM 0–2)	29.6% vs. 19.0% RR: 1.56 [1.19; 2.03] RR: 0.64 [0.49; 0.84][c] p = 0.001 Probability: indication	Outcome category: serious/severe symptoms / late complications $0.75 \leq CI_u < 0.90$ Added benefit; extent: considerable
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

Table 16: 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]
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
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; SPI: Sleep Problem Index; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results which were factored into the overall conclusion on the extent of added benefit.

Table 17: 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 ▪ Patient-reported symptoms (POEM 0–2): indication of added benefit – extent: considerable	–
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	

Overall, both favourable and unfavourable effects were found for abrocitinib in comparison with dupilumab. For each of the outcomes of remission and patient-reported symptoms, an indication of considerable added benefit was found. No subgroup analyses are available for the outcome of remission. 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 with moderate-to-severe atopic dermatitis who are candidates for systemic therapy, there is an indication of considerable added benefit of abrocitinib in comparison with the ACT of dupilumab.

Table 18 summarizes the result of the assessment of the added benefit of abrocitinib in comparison with the ACT.

Table 18: 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 therapy[b]	Dupilumab (possibly combined with TCS and/or TCI)	Indication of considerable 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 therapy. 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 above assessment deviates from the assessment by the company, which derived an indication of minor added benefit of abrocitinib in comparison with dupilumab.

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

References for English extract

Please see full dossier assessment for full reference list.

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

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