Abrocitinib
(atopic dermatitis in adolescents ≥ 12 years)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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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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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSA	body surface area
cDLQI	Children's Dermatology Life Quality Index
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EMA	European Medicines Agency
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)
NRS	numerical rating scale
PT	Preferred Term
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TCI	topical calcineurin inhibitors
TCS	topical glucocorticoids
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has 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 24 April 2024.

Research question

The aim of the present report is to assess the added benefit of abrocitinib in comparison with the appropriate comparator therapy (ACT) dupilumab in adolescents 12 years and older with moderate-to-severe atopic dermatitis who are candidates for systemic therapy.

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

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

Therapeutic indication	**ACT[b]**
Adolescents 12 years and older with moderate-to-severe atopic dermatitis who are candidates for systemic therapy	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. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TCI: topical calcineurin inhibitors; TCS: topical glucocorticoids	

The company followed the specification of the G-BA by designating dupilumab as the ACT.

The assessment is 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 treatment duration of 24 weeks are used for the derivation of the added benefit.

Results

The check of completeness of the study pool revealed no RCT for the direct comparison of abrocitinib in comparison with the ACT dupilumab for adolescents 12 years and older with moderate-to-severe atopic dermatitis who are candidates for systemic therapy.

Data presented by the company

Since the company also did not identify any RCT for the direct comparison of abrocitinib versus the ACT dupilumab in adolescents aged 12 years and older with moderate-to-severe atopic dermatitis who are candidates for systemic therapy, it used the JADE DARE study with adults,

already known from dossier assessment A22-06 and the associated addendum A22-60, to assess the added benefit of abrocitinib in adolescents by conducting an evidence transfer. In addition, the company presented analyses of the placebo-controlled JADE TEEN study with adolescents in order to examine the prerequisites for evidence transfer from adults to adolescents.

The data presented by the company are not suitable for deriving conclusions on the added benefit of abrocitinib in comparison with dupilumab in adolescents with moderate-to-severe atopic dermatitis who are candidates for systemic therapy. Below, the data presented by the company are described, and afterwards the reasons for its unsuitability for deriving added benefit for the present research questions are provided.

JADE DARE study

The JADE DARE study has already been used in the dossier assessment A22-06 and the associated addendum A22-60 for the assessment of the added benefit of abrocitinib in comparison with the ACT for moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy. The JADE DARE study is a double-blind RCT comparing abrocitinib and dupilumab. The treatment duration was 26 weeks. A total of 727 patients were assigned to treatment with abrocitinib 200 mg once daily (N = 362) or dupilumab 300 mg every 2 weeks (N = 365). The abrocitinib dosage of 100 mg, which is also approved, was not investigated in the JADE DARE study.

For the entire treatment duration, patients had to apply emollients daily and topical drug treatment to areas with active lesions.

JADE TEEN study

The JADE TEEN study is a double-blind RCT comparing abrocitinib and placebo with a treatment duration of 12 weeks. The study included patients aged 12 to 17 years with moderate-to-severe atopic dermatitis.

Overall, 287 patients were included in the JADE TEEN study and randomly allocated in a 1:1 ratio either to treatment with abrocitinib 200 mg (N = 96), abrocitinib 100 mg (N = 95), or placebo (N = 96).

In the JADE TEEN study, the allocation to the two intervention arms and thus the determination of the starting dose was carried out without taking into account patient-specific characteristics such as weight or risk factors including increased risk of venous thromboembolism, serious adverse cardiovascular events and malignant diseases in accordance with the specifications in the Summary of Product Characteristics (SPC). In Module 4 A, the company presents only the 200 mg arm and the placebo arm on the intervention side.

For the entire treatment duration, all patients had to apply emollients at least once daily and topical drug treatment to areas with active lesions.

Assessment of the company's data

JADE TEEN study unsuitable for the benefit assessment

The JADE TEEN study is unsuitable for answering the research question of the present benefit assessment. The ACT dupilumab (possibly in combination with topical glucocorticoids or calcineurin inhibitors) specified by the G-BA was not implemented, as the patients in the control arm received placebo in combination with a topical background therapy. In addition, the treatment duration of the JADE TEEN study used by the company is 12 weeks and therefore does not fulfil the minimum treatment duration of 24 weeks in the present therapeutic indication.

Results of the JADE DARE study are not transferable to adolescents

Under certain circumstances, results can be transferred from one population to another one for which no or only insufficient data are available. The company transferred the results of the JADE DARE study in adults to the target population of adolescents in the present therapeutic indication. In Module 4 A, the company presents the results of the JADE TEEN study for the population of adolescents with moderate-to-severe atopic dermatitis who are candidates for systemic therapy in order to verify transferability.

In the present data constellation, however, it is not possible to transfer the results from adults in the JADE DARE study to adolescents. While the pathogenesis and clinical picture of atopic dermatitis as well as the mechanism of action of abrocitinib are sufficiently similar between adults and adolescents, further prerequisites for transferring results from adults to the adolescent target population are not fulfilled. The JADE DARE and JADE TEEN studies used by the company differed not only with regard to the age of the patient population and the treatment duration, but also in particular with regard to the comparator used: the JADE DARE study only investigated the comparison with placebo (+ background therapy) and not with the ACT dupilumab (+ background therapy).

Irrespective of this, key outcomes (remission [Eczema Area and Severity Index 100, SCORing Atopic Dermatitis 100]; SCORing atopic dermatitis improvement by 90% [SCORAD 90] and patient-reported symptoms [Patient Oriented Eczema Measure 0]), which formed the basis for the positive conclusion of dossier assessment A22-06 with the associated addendum A22-60 and the decision on the procedure for abrocitinib in adult patients, did not show any statistically significant effects in the JADE TEEN study. Only the patient-reported symptoms in the operationalization Patient Oriented Eczema Measure 0 to 2 showed a statistically significant effect in favour of abrocitinib in the JADE TEEN study. The results relate exclusively to the comparison with placebo (+ background therapy) and not with the ACT dupilumab

(+ background therapy). The company also did not conduct any information retrieval on studies with the ACT. With such an information retrieval, the company could identify studies in adolescents in which dupilumab is not directly compared with abrocitinib, but which could in principle provide data on the ACT dupilumab for the present research question. It should be noted that at least 1 RCT on dupilumab in comparison with placebo in adolescents exists in the form of the AD-1526 study known from dossier assessment A19-75. However, it is unclear whether the JADE TEEN and AD-1526 studies are sufficiently similar to support the evidence transfer. At the very least, there are differences in the study duration and background therapy.

Results on added benefit

In its dossier, the company did not present any suitable data for the assessment of the added benefit of abrocitinib in comparison with the ACT dupilumab for adolescents 12 years and older with moderate-to-severe atopic dermatitis who are candidates for systemic therapy. There is no hint of an added benefit of abrocitinib in comparison with the ACT dupilumab; an added benefit is therefore not proven.

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

Table 3 summarizes the result of the assessment of the added benefit of abrocitinib in comparison with the ACT.

Table 3: Abrocitinib[a] – probability and extent of added benefit

Therapeutic indication	ACT[b]	Probability and extent of added benefit
Adolescents 12 years and older with moderate-to-severe atopic dermatitis who are candidates for systemic therapy	Dupilumab (if applicable, in combination with TCS and/or TCI)	Added benefit not proven
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. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TCI: topical calcineurin inhibitors; TCS: topical glucocorticoids		

The G-BA decides on the added benefit.

[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].

I 2 Research question

The aim of the present report is to assess the added benefit of abrocitinib in comparison with the ACT dupilumab in adolescents 12 years and older with moderate-to-severe atopic dermatitis who are candidates for systemic therapy.

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

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

Therapeutic indication	**ACT[b]**
Adolescents 12 years and older with moderate-to-severe atopic dermatitis who are candidates for systemic therapy	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 [3]. b. Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TCI: topical calcineurin inhibitors; TCS: topical glucocorticoids	

The company followed the specification of the G-BA by designating dupilumab as the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum treatment duration of 24 weeks are used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

I 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: 15 February 2024)
- bibliographical literature search on abrocitinib (last search on 15 February 2024)
- search in trial registries / trial results databases for studies on abrocitinib (last search on 15 February 2024)
- search on the G-BA website for abrocitinib (last search on 16 February 2024)

To check the completeness of the study pool:

- search in trial registries for studies on abrocitinib (last search on 10 May 2024); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of completeness of the study pool revealed no RCT for the direct comparison of abrocitinib in comparison with the ACT dupilumab for adolescents 12 years and older with moderate-to-severe atopic dermatitis who are candidates for systemic therapy. For the assessment of the added benefit of abrocitinib in adolescents, the company therefore used the JADE DARE study with adults already known from dossier assessment A22-06 [4] and the associated addendum A22-60 [5] by conducting an evidence transfer.

In addition, the company presented analyses of the placebo-controlled JADE TEEN study [6-10] with adolescents in order to examine the prerequisites for evidence transfer from adults to adolescents. The company identified the JADE TEEN study from its own study pool as the best available evidence for adolescents in the present therapeutic indication from its point of view (see Section I 3.2). The company did not conduct any information retrieval for studies with adolescents for the ACT dupilumab.

The data presented by the company are not suitable for deriving conclusions on the added benefit of abrocitinib in comparison with dupilumab in adolescents with moderate-to-severe atopic dermatitis who are candidates for systemic therapy. Below, the data presented by the company are described, and afterwards the reasons for its unsuitability for deriving added benefit for the present research questions are provided.

I 3.1 Data presented by the company

JADE DARE study

The JADE DARE study has already been used in the dossier assessment A22-06 [4] and the associated addendum A22-60 [5] for the assessment of the added benefit of abrocitinib in

comparison with the ACT for moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy. The JADE DARE study is a double-blind RCT comparing abrocitinib and dupilumab. The treatment duration was 26 weeks. A total of 727 patients were assigned to treatment with abrocitinib 200 mg once daily (N = 362) or dupilumab 300 mg every 2 weeks (N = 365). The abrocitinib dosage of 100 mg, which is also approved, was not investigated in the JADE DARE study.

For the entire treatment duration, patients had to apply emollients at least twice daily and moderate-potency topical glucocorticoids (TCS) once daily to areas with active lesions. On areas of intolerance or thin skin, low-potency TCS, topical calcineurin inhibitors (TCI) or phosphodiesterase (PDE) 4 inhibitors could be used. Background therapy with TCS, TCI, or any PDE4 inhibitors was de-escalated or reinitiated according to a defined regimen. 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. [11] was allowed after Week 4 if deemed necessary by the investigator.

See dossier assessment A22-06 [4] for a detailed description of the study and intervention characteristics of the already known JADE DARE study.

JADE TEEN study

The JADE TEEN study is a double-blind RCT comparing abrocitinib and placebo with a treatment duration of 12 weeks. Afterwards, patients had the option of participating in the extension study JADE EXTEND [12] administering 100 mg or 200 mg abrocitinib.

The JADE TEEN study included patients aged 12 to 17 years with moderate-to-severe atopic dermatitis. Severity of disease was defined based on the following baseline criteria: ≥ 10% of body surface area (BSA) affected; Investigator Global Assessment (IGA) ≥ 3; Eczema Area and Severity Index (EASI) ≥ 16, and itching with a score of ≥ 4 on the Peak Pruritus Numerical Rating Scale (NRS). Furthermore, the patients had to have either responded inadequately to topical drug treatments for atopic dermatitis for at least 4 consecutive weeks within 6 months prior to the screening or had to have received a systemic therapy for the treatment of atopic dermatitis or a systemic therapy had to be considered according to medical judgement. It is not clear from the available information how an inadequate response was defined or what criteria were used to determine eligibility for systemic therapy.

Overall, 287 patients were included in the JADE TEEN study and randomly allocated in a 1:1 ratio either to treatment with abrocitinib 200 mg (N = 96), abrocitinib 100 mg (N = 95), or placebo (N = 96). The stratification factor was the severity of disease (IGA 3 vs. IGA 4).

In principle, both abrocitinib doses used in the JADE TEEN study (100 mg and 200 mg once daily each) are approved for the treatment of adolescents according to the SPC, whereby the recommended starting dose for adolescents weighing less than 59 kg is 100 mg once daily; for

adolescents weighing 59 kg or more, a starting dose of 100 mg or 200 mg once daily may be indicated [3]. According to the SPC, the starting dose can be reduced or increased based on tolerance and efficacy. Regardless of age, the choice of starting dose should be made based on individual patient characteristics such as an increased risk of venous thromboembolism, severe adverse cardiovascular events and malignant diseases. Further, patients on maintenance therapy should receive the lowest effective dose. In the JADE TEEN study, the allocation to the two intervention arms and thus the determination of the starting dose was carried out without taking into account patient-specific characteristics such as weight or risk factors. However, due to the exclusion criteria, it was largely not possible for patients with risk factors to participate in the JADE TEEN study. In Module 4 A, the company presents only the 200 mg arm and the placebo arm on the intervention side. To assess the lack of individualized dosing according to body weight, see Section I 3.2.

Throughout the entire treatment duration, all patients had to apply emollients at least twice daily as background therapy. In areas with active lesions, moderate-potency TCS were applied once daily, and in areas with intolerance or thin skin, low-potency TCS, TCI, or PDE4 inhibitors. Background therapy with TCS, TCI, or any PDE4 inhibitors was de-escalated or reinitiated according to a defined regimen (see Table 7 of the full dossier assessment). According to the study protocol, a treatment escalation with high-potency TCS, systemic glucocorticoids or other systemic therapies was not planned in the study.

The primary outcomes of the study were an IGA 0-1 with simultaneous improvement of the IGA by ≥ 2 points at week 12 and EASI 75 at week 12. Additionally, outcomes in the categories of morbidity, health-related quality of life and side effects were recorded.

For a characterization of the JADE TEEN study, see also Table 6 and Table 7 in I Appendix B of the full dossier assessment.

Approach of the company

To assess the added benefit, the company took the total population of the JADE DARE study on adults into account and transferred its results to the target population of adolescents in the present therapeutic indication. The company justified the need for evidence transfer on the grounds that the JADE TEEN study with a treatment duration of 12 weeks, which it additionally presented in Module 4 A, was considered too short in the context of the benefit assessment and that moreover the study was placebo-controlled. Nevertheless, the company believes that the results of the JADE TEEN study can be used to verify the transferability of the results of the JADE DARE study to the adolescent target population, as in its view the requirements for evidence transfer are met. With reference to the European Medicines Agency (EMA), it cited various criteria [13,14]. It stated for instance that the mechanism of action of abrocitinib in adults and adolescents is comparable and the pathogenesis and clinical

picture are sufficiently similar. Furthermore, it stated that the ACT specified by the G-BA is identical for adults and adolescents, and an added benefit of abrocitinib in the present therapeutic indication has been established for adults. The company also stated that there are no effect modifications due to age in the JADE DARE study and there are mostly sufficiently large effects in the JADE TEEN study. The company concluded the latter by comparing only the intervention arms with abrocitinib at a dose of 200 mg of the JADE DARE and JADE TEEN studies at week 12.

In addition, the company justified its exclusive consideration of the JADE TEEN study on adolescents with the fact that in this study, in contrast to the JADE MONO 1 [15] and JADE MONO 2 [16] studies, which also included adolescents, a background therapy was administered analogue to the JADE DARE study, and therefore the JADE TEEN study, in connection with the transfer of the results of the JADE DARE study, provides the best available evidence for adolescents 12 years and older with moderate-to-severe atopic dermatitis who are candidates for systemic therapy.

I 3.2 Assessment of the data and approach of the company

The data presented by the company are not suitable for the benefit assessment of abrocitinib in comparison with the ACT dupilumab in adolescents with moderate-to-severe atopic dermatitis who are candidates for systemic therapy. This is justified below.

JADE TEEN study unsuitable for the benefit assessment

In agreement with the company, the JADE TEEN study is not suitable for answering the research question of the present benefit assessment because, on the one hand, the appropriate comparator therapy has not been implemented. In the JADE TEEN study, patients in the control arm received placebo in combination with a topical background therapy (see Table 7 of the full dossier assessment). However, the G-BA specified dupilumab (possibly in combination with TCS and/or TCI) as the ACT. On the other hand, the treatment duration of the JADE TEEN study used by the company is 12 weeks and therefore does not fulfil the minimum treatment duration of 24 weeks in the present therapeutic indication. A treatment duration of 12 weeks is altogether too short to assess the long-term effects of abrocitinib on the chronic inflammatory course of atopic dermatitis.

Further uncertainties

Suitability of patients for systemic therapy

According to the checklist for establishing the indication for systemic therapy in adolescents (Checkliste “Indikationsstellung für die Systemtherapie: Jugendliche”) as part of the S3 guideline on atopic dermatitis, various criteria must be checked for the initiation of systemic therapy or when switching to another systemic therapy [17]. Accordingly, a systemic therapy is suitable for patients if there is a relevant objective severity, a significant subjective

burden, and a lack of treatment response. The European guideline, in contrast, does not specify any strict subjective criteria for establishing the indication for systemic therapy [18-20].

The criteria for inclusion in the JADE TEEN study (see Section I 3.1) already fulfil the requirements for relevant objective severity and lack of treatment response. To assess the relevant subjective burden, 3 criteria are listed in accordance with the above-mentioned checklist: (Children's) Dermatology Life Quality Index (cDLQI DLQI) > 10, itching > 6 on a visual analogue scale (VAS) or NRS from 0 to 10, or relevant night-time sleep disturbance due to itching/eczema. No specific threshold value is specified for night-time sleep disturbance, above which a relevant disturbance can be assumed. In addition, no separate analyses of sleep disorders are available for the JADE TEEN study. This criterion is therefore not considered further below. IQWiG calculations based on means and standard deviations and assuming normal distribution in the study population show that over 71% of JADE TEEN participants had a baseline cDLQI ≥ 11. Over 71% of patients had a peak pruritus ≥ 7 on a NRS at baseline. The patient population with a cDLQI ≥ 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. Despite this uncertainty, it is generally assumed that a systemic therapy is an option for the JADE TEEN study population.

Abrocitinib dosage independent of body weight

As described above, for the JADE TEEN study, the company only presented the study arm in which abrocitinib was administered at a dose of 200 mg on the intervention page in Module 4 A. The reason for this is presumably that abrocitinib was only used at a dose of 200 mg in the JADE DARE study and the company wanted to create better comparability of the intervention arms of the JADE DARE and JADE TEEN studies for the evidence transfer it carried out.

According to the SPC, the starting dose for adolescents depends in particular on body weight. According to IQWiG calculations based on means and standard deviations and assuming normal distribution, approximately 48% of patients in the 200 mg abrocitinib arm of the JADE TEEN study weighed less than 59 kg and therefore did not receive the approval-compliant starting dose for this age group. Furthermore, the JADE TEEN study did not allow dose modification based on tolerance and effectiveness. Regarding the timing of treatment modification, no clear criteria have been established, particularly not after treatment response. However, it is assumed that no larger-scale dose modifications are usually necessary within a treatment period of 12 weeks, as in the JADE TEEN study. Therefore, the limitation of no dose modification options remains without consequence for the present assessment.

Results of the JADE DARE study are not transferable to adolescents

As described, the company transferred the results of the JADE DARE study in adults to the target population of adolescents in the present therapeutic indication. Under certain circumstances, results can be transferred from one population to another one for which no or only insufficient data are available. In Module 4 A, the company presents the results of the JADE TEEN study for the population of adolescents with moderate-to-severe atopic dermatitis who are candidates for systemic therapy in order to verify transferability, limiting the presentation to the 200 mg abrocitinib arm and the placebo arm. The company did not consider other RCTs in the therapeutic indication that also included comparisons of abrocitinib versus placebo (the company mentioned the JADE MONO 1 and JADE MONO 2 studies, see Section I 3.1) when transferring the results of the JADE DARE study with adult patients. Due to the fact that only in the JADE TEEN study a background therapy analogous to the JADE DARE study was administered, the company's approach of only considering the JADE TEEN study for adolescents appears basically comprehensible.

In the present data constellation, however, it is not possible to transfer the results from adults in the JADE DARE study to adolescents. While the pathogenesis and clinical picture of atopic dermatitis as well as the mechanism of action of abrocitinib are sufficiently similar between adults and adolescents [21-24], further prerequisites for transferring results from adults to the adolescent target population are not fulfilled. The JADE DARE and JADE TEEN studies used by the company differed not only with regard to the age of the patient population and the treatment duration, but also in particular with regard to the comparator used: the JADE DARE study only investigated the comparison with placebo (+ background therapy) and not with the ACT dupilumab (+ background therapy).

Further comments on the transfer carried out by of the company

Key outcomes for the outcome category of morbidity (remission [EASI 100, SCORing Atopic Dermatitis 100]; SCORing-Atopic-Dermatitis improvement by 90% [SCORAD 90] as well as patient-reported symptoms [Patient Oriented Eczema Measure 0]), which formed the basis for the positive conclusion of the dossier assessment A22-06 [4] with the associated addendum A22-60 [5] and the decision on the procedure for Abrocitinib in adult patients [25,26], showed no statistically significant effects in the JADE TEEN study. Only the patient-reported symptoms in the operationalization Patient Oriented Eczema Measure 0 to 2 showed a statistically significant effect in favour of abrocitinib in the JADE TEEN study.

In addition, the JADE TEEN study showed a statistically significant effect in favour of abrocitinib for the outcome of pruritus (improvement in peak pruritus NRS by ≥ 4 points) that was relevant for the benefit assessment, while a statistically significant effect to the disadvantage of abrocitinib was shown for the outcome of nausea (preferred term [PT], adverse events [AEs]). The results relate exclusively to the comparison with placebo (+ background therapy)

and not with the ACT dupilumab (+ background therapy). The company itself based its assessment only on the comparison of the abrocitinib arms of both studies, i.e. neither against a background therapy nor against the ACT dupilumab. From the JADE DARE study, the company considered the abrocitinib arm without restriction to the youngest age stratum (see below). The company also did not conduct any information retrieval on studies with the ACT. With such an information retrieval, the company could identify studies in adolescents in which dupilumab is not directly compared with abrocitinib, but which could in principle provide data on the ACT dupilumab for the present research question. It should be noted that there is at least 1 RCT on dupilumab in adolescents, the AD-1526 study known from dossier assessment A19-75 [27]. However, it is unclear whether the JADE TEEN and AD-1526 studies are sufficiently similar to support the evidence transfer. At the very least, there are differences in the study duration and background therapy.

It should also be noted that the best possible approximation of the target population is the youngest age stratum (≥ 18 to < 40 years) of the JADE DARE study. This also applies against the background that in the JADE DARE study, contrary to the company's assessment (see Section I 3.1), a significant effect modification by age occurred in addendum A22-60 for the outcome of patient-reported symptoms, operationalized as Patient Oriented Eczema Measure 0, and the added benefit was derived separately according to age [5]. For the relevant age stratum (≥ 18 to < 40 years), neither information on patient characteristics nor analyses on all patient-relevant outcomes are available in dossier assessment A22-06 and the associated addendum A22-60. A comparative juxtaposition of patient characteristics and results for the relevant age stratum is therefore not possible or only possible to a limited extent. However, this would be necessary to assess whether the results from the JADE DARE study can be transferred to the target population.

Furthermore, it should be noted that in the JADE DARE study, abrocitinib and dupilumab were used only at the higher approved dosage (200 mg and 300 mg respectively). No data are available for the equally approved dosages of 100 mg (abrocitinib) and 200 mg (dupilumab), which according to the SPC should be administered to adolescents with a body weight of < 59 kg/< 60 kg.

In summary, based on the available data, it is not possible to transfer the results from adults in the JADE DARE study to adolescents.

I 4 Results on added benefit

In its dossier, the company did not present any suitable data for the assessment of the added benefit of abrocitinib in comparison with the ACT dupilumab for adolescents 12 years and older with moderate-to-severe atopic dermatitis who are candidates for systemic therapy. There is no hint of an added benefit of abrocitinib in comparison with the ACT dupilumab; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of the added benefit of abrocitinib in comparison with the ACT.

Table 5: Abrocitinib[a] – probability and extent of added benefit

Therapeutic indication	**ACT[b]**	**Probability and extent of added benefit**
Adolescents 12 years and older with moderate-to-severe atopic dermatitis who are candidates for systemic therapy	Dupilumab (if applicable, in combination with TCS and/or TCI)	Added benefit not proven
a. Abrocitinib may be used as monotherapy or with other drugs for topical use in atopic dermatitis [3]. b. Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TCI: topical calcineurin inhibitors; TCS: topical glucocorticoids		

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit of abrocitinib in comparison with dupilumab in adolescents 12 years and older with moderate-to-severe atopic dermatitis who are candidates for systemic therapy.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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