IQWiG Reports – Commission No. A21-116

Upadacitinib (atopic dermatitis) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Upadacitinib (atopische Dermatitis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 November 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Upadacitinib (atopic dermatitis) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
1 September 2021

Internal Commission No.
A21-116

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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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Keywords: Upadacitinib, Dermatitis – Atopic, Benefit Assessment, NCT03738397, NCT03569293, NCT03607422, NCT03568318

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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
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EMA	European Medicines Agency
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLM	generalized linear model
HN-PGIS	Head and Neck-Patient Global Impression of Severity
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MI	multiple imputation
NRI	non-responder imputation
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
TCI	topical calcineurin inhibitors
TCS	topical glucocorticoids
vIGA-AD	validated Investigator Global Assessment for Atopic Dermatitis
WP-NRS	Worst Pruritus Numerical Rating Scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug upadacitinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 September 2021.

Research question

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

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

Table 2: Research question of the benefit assessment of upadacitinib

Therapeutic indication	**ACT**[a]
Moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy[b]	Dupilumab (possibly in combination with TCS and/or TCI)
a. Presentation of the ACT specified by the G-BA. b. According to the approval, the therapeutic indication comprises those patients who are candidates for systemic therapy. For the determination of the ACT, adults and adolescents 12 years and older with moderate to severe atopic dermatitis are considered for whom long-term/continuous systemic therapy is indicated, as the drug upadacitinib is to be used as continuous therapy and is therefore only an option for patients for whom long-term/continuous systemic therapy is indicated. 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 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

The study pool for the benefit assessment of upadacitinib consists of the RCT M16-046 (hereinafter referred to as "Heads Up" study). This study included only adults with moderate to severe atopic dermatitis. There are no data corresponding to the research question of the present benefit assessment on adolescents 12 years and older who are also comprised by the therapeutic indication.

In addition, the company presented supplementary analyses on adolescents 12 years and older from the 3 pivotal approval studies M16-045 (hereinafter referred to as "Measure Up 1" study), M18-891 (hereinafter referred to as "Measure Up 2" study) and M16-047 (hereinafter referred to as "AD Up" study) and used these analyses to transfer the results of the Heads Up study from adults to adolescents. In the present data constellation, an evidence transfer to adolescent patients is not possible, however (see below).

In the following, adults and adolescents 12 years and older are addressed in separate research subquestions:

- Subquestion 1: adults with moderate to severe atopic dermatitis who are candidates for systemic therapy
- Subquestion 2: adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy

Subquestion 1: adults with moderate to severe atopic dermatitis who are candidates for systemic therapy

Study design

Study design, patient population and interventions

The Heads Up study is a randomized, double-blind RCT comparing upadacitinib with dupilumab over 24 weeks. It investigated adults aged 18 to 75 years who had had moderate to severe atopic dermatitis for at least 3 years. In addition, patients had to have a history inadequate response to topical treatment with topical glucocorticoids (TCS) and/or topical calcineurin inhibitors (TCI) or to systemic therapy within 6 months prior to randomization, or topical treatments were otherwise medically inadvisable (e.g. because of side effects).

348 patients were randomly allocated to the upadacitinib arm and 344 patients to the dupilumab arm.

Patients in the intervention arm received 30 mg upadacitinib daily. This dosage is approved in the therapeutic indication. In the comparator arm, dupilumab was administered in compliance with the Summary of Product Characteristics (SPC). In the course of the study, treatment escalation (referred to as "rescue therapy" by the company) could be provided at the discretion of the investigator; if possible initially with topical medications such as TCS and/or TCI. Patients who did not respond adequately within 7 days of topical treatment were to receive systemic therapy and phototherapy at the discretion of the investigator; this led to the permanent discontinuation of the study medication, however.

Primary outcome of the study was the Eczema Area and Severity Index (EASI) 75. Patient-relevant outcomes on morbidity and side effects were additionally recorded. Outcomes from the category of health-related quality of life were not recorded.

Upadacitinib dosage used in the Heads Up study

In the Heads Up study, all patients, regardless of age, received upadacitinib exclusively in the 30 mg dose. This meant that it was neither possible to start treatment with the also approved dose of 15 mg nor was it permitted to adjust the dose to the 15 mg dose during the course of the study. In the Heads Up study, patients ≥ 65 years of age thus did not receive the 15 mg dose, which is in compliance with the approval for this age group. However, since only a small proportion of the study population (5%) was ≥ 65 years of age, this deviation from the SPC has no impact on the present assessment.

In patients aged between 18 and 64 years, both the 15 mg and the 30 mg dose of upadacitinib can be used according to the SPC, with no specific recommendations regarding the cases in which the 15 mg or 30 mg doses should be administered. Since it is assumed that the 30 mg dose of upadacitinib is more likely to be administered in the presence of severe atopic dermatitis and since, according to the EASI classification of the severity levels, most patients in the study population (about 77%) had severe disease, it is assumed in summary that a dose of 30 mg at baseline was appropriate for the majority of the study population. However, due to the uncertainty and the fact that no dose adjustment to the lower dose (15 mg) was allowed during the course of the study in case of response to treatment with upadacitinib, the certainty of conclusions is reduced. Thus, at most hints, e.g. of an added benefit, can be derived for all outcomes on the basis of the effects shown in the Heads Up study.

Conclusion on added benefit is only possible for patients for whom 30 mg is the appropriate dose

As described above, all patients in the intervention arm of the Heads Up study received upadacitinib at a dose of 30 mg, and it is assumed that 30 mg was the correct dose for the majority of patients, at least at the start of the study. No results are available in comparison with the ACT dupilumab for adult patients for whom 15 mg is the appropriate dose.

The comparison of the results of the 15 mg and 30 mg doses of upadacitinib for adults from the approval studies Measure Up 1, Measure Up 2 and AD Up over a treatment period of 16 weeks shows a dose-dependent efficacy of upadacitinib. Based on the observed differences, the effects can be expected to be smaller or absent under treatment with upadacitinib at the 15 mg dose compared with the ACT dupilumab than under treatment with a 30 mg dose.

In the present data situation, a conclusion on the added benefit is therefore only drawn for patients for whom 30 mg is the appropriate dose.

Risk of bias

The risk of bias across outcomes for the Heads Up study is rated as low.

The risk of bias of the results of the following outcomes is rated as low: all-cause mortality, remission (EASI 100) and itching (Worst Pruritus Numerical Rating Scale [WP-NRS]), as well as patient-reported symptoms (Head and Neck-Patient Global Impression of Severity

[HN-PGIS]). The risk of bias of the results for all outcomes of the category of side effects is rated as high. This is due to different observation durations between the study arms.

Results

Mortality

All-cause mortality

For the outcome of all-cause mortality, one death occurred in the upadacitinib arm. No statistically significant difference was shown between upadacitinib and dupilumab. This results in no hint of an added benefit of upadacitinib in comparison with dupilumab; an added benefit is therefore not proven.

Morbidity

Symptoms – remission (EASI 100) and itching (WP-NRS 0)

A statistically significant difference in favour of upadacitinib in comparison with dupilumab was shown for the outcome of symptoms – remission (EASI 100) and itching (WP-NRS 0). In each case, this results in a hint of an added benefit of upadacitinib in comparison with dupilumab.

Symptoms – patient-reported symptoms (HN-PGIS 0)

A statistically significant difference in favour of upadacitinib in comparison with dupilumab was shown for the outcome of patient-reported symptoms (HN-PGIS 0). This results in a hint of an added benefit of upadacitinib in comparison with dupilumab.

Health-related quality of life

No outcomes in the outcome category of health-related quality of life were recorded in the Heads Up study. This results in no hint of an added benefit of upadacitinib in comparison with dupilumab in this outcome category; an added benefit is therefore not proven.

Side effects

Overall rates of serious adverse events (SAEs) and discontinuation due to adverse events (AEs)

No statistically significant difference between upadacitinib and dupilumab was shown for the outcomes of SAEs and discontinuation due to AEs. This results in no hint of greater or lesser harm from upadacitinib in each case; greater or lesser harm is therefore not proven.

Overall rates of severe AEs (Common Terminology Criteria for Adverse Events; [CTCAE] grade ≥ 3)

A statistically significant difference to the disadvantage of upadacitinib in comparison with dupilumab was shown for the outcome of severe AEs. However, there is an effect modification by the characteristic of sex. For women, this results in a hint of greater harm from upadacitinib in comparison with dupilumab. For men, there is no hint of greater or lesser harm from

upadacitinib in each case; greater or lesser harm for men is therefore not proven for this outcome.

Infections

A statistically significant difference to the disadvantage of upadacitinib in comparison with dupilumab was shown for the outcome of infections. However, there is an effect modification by the characteristic of age. For patients ≥ 40 years of age, this results in a hint of greater harm from upadacitinib in comparison with dupilumab for the outcome of infections. For patients < 40 years of age, there is no hint of greater or lesser harm from upadacitinib; greater or lesser harm is therefore not proven for patients < 40 years of age for this outcome.

Serious infections

No statistically significant difference between upadacitinib and dupilumab was shown for the outcome of serious infections. This results in no hint of greater or lesser harm from upadacitinib; greater or lesser harm is therefore not proven.

Conjunctivitis (PT, AE)

A statistically significant difference in favour of upadacitinib in comparison with dupilumab was shown for the outcome of conjunctivitis (System Organ Class [SOC], AE). This results in a hint of lesser harm from upadacitinib in comparison with dupilumab.

Eye disorders (SOC, AE)

A statistically significant difference in favour of upadacitinib in comparison with dupilumab was shown for the outcome of eye disorders (SOC, AE). However, there is an effect modification by the characteristic of disease severity. For patients with a validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) 4, this results in a hint of lesser harm from upadacitinib in comparison with dupilumab. For patients with a vIGA-AD 3, there is no hint of greater or lesser harm from upadacitinib; greater or lesser harm is therefore not proven for patients with a vIGA-AD 3.

Acne (Preferred Term [PT], AE)

A statistically significant difference to the disadvantage of upadacitinib in comparison with dupilumab was shown for the outcome of acne (PT, AE). This results in a hint of greater harm from upadacitinib in comparison with dupilumab.

Subquestion 2: adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy

Approach of the company

The company did not identify any RCTs conducted in adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy, and comparing upadacitinib against the ACT dupilumab. The company therefore used the Heads Up study in adults for the derivation of the added benefit for adolescents, conducting an evidence transfer.

To check the prerequisites for an evidence transfer to adolescents, the company presented analyses on adolescents (12 to 17 years of age) of the 3 studies Measure Up 1, Measure Up 2 and AD Up as supplementary information.

Study characteristics of Measure Up 1, Measure Up 2 and AD Up

All 3 studies are RCTs with a double-blind treatment phase of 16 weeks comparing upadacitinib in dosages of 15 mg and 30 mg daily against placebo.

They included patients aged 12 to 75 years with moderate to severe atopic dermatitis. Following the double-blind treatment phase, patients entered a single-blind extension phase with either 15 mg or 30 mg upadacitinib; patients in the original placebo arms were also randomized to one of the 2 upadacitinib arms.

In the AD-Up study, patients additionally received class II TCS and/or TCI on areas with active lesions as background therapy at the beginning of the study medication and until the active lesions were under control, but no longer than up to and including treatment week 3. Starting from week 4, treatment escalation ("rescue therapy") was permitted in all 3 studies, initially with topical therapies and, in case of inadequate response, also with systemic therapies.

Of the total of 847 patients included in the Measure Up 1 study, 42 adolescents each were randomly assigned to the 15 mg upadacitinib arm and to the 30 mg upadacitinib arm, and 40 adolescents to the placebo arm. Of the total 836 patients included in the Measure Up 2 study, 33 adolescents were randomly assigned to the 15 mg upadacitinib arm, 35 adolescents to the 30 mg upadacitinib arm, and 36 adolescents to the placebo arm. Of the total of 901 patients included in the AD Up study, 39 adolescents were randomly assigned to the 15 mg upadacitinib arm, 37 adolescents to the 30 mg upadacitinib arm, and 40 adolescents to the placebo arm.

Results of the Heads Up study are not transferable to adolescents

The company conducted an evidence transfer to adolescents by transferring the results of the Heads Up study in adults to adolescents. It additionally considered the analyses on adolescents from the studies Measure Up 1, Measure Up 2 and AD Up. For this purpose, it used the 15 mg upadacitinib arms and the placebo arms because 15 mg is the only approved dose for adolescents. The company did not present any data for adolescents on the comparator therapy dupilumab and also had not searched for data on dupilumab.

In the present data constellation, it is not possible to transfer the results from adults in the Heads Up study to adolescents. As described above, upadacitinib was administered only in the 30 mg dose in the Heads Up study, although upadacitinib is also approved in the 15 mg dose for adults. Thus, data are only available for adults for whom a dose of 30 mg is appropriate. Due to the dose-dependent efficacy of upadacitinib, the derivation of the added benefit in the present benefit assessment is only conducted for patients for whom the 30 mg dose is the appropriate dose of upadacitinib. No data are available for adults for whom the 15 mg dose of upadacitinib

is the appropriate dose. Since only the 15 mg dose is approved for adolescents, a transfer of the results from adults to adolescents is not possible in this data constellation.

Results

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

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

Subquestion 1: adults with moderate to severe atopic dermatitis who are candidates for systemic therapy

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

The overall consideration shows both positive and negative effects of upadacitinib in comparison with dupilumab, partly only for subgroups. The effect modifications by the characteristics of age and severity only occurred in non-serious/non-severe side effect outcomes and are therefore not considered further. The effect modification by the characteristic of sex, however, occurred in a serious/severe side effect outcome. For this reason, the balancing of positive and negative effects is conducted separately for men and women in the following.

Due to the limitations of the Heads Up study described above, the following overall conclusions on the added benefit only apply to adults for whom 30 mg upadacitinib is the appropriate dose. No data are available for adults for whom 15 mg upadacitinib is the appropriate dose.

Women

The positive effects, each with major extent, for the symptom outcomes of remission and itching are decisive for the conclusion on the added benefit for women. There is another positive effect with considerable extent for the outcome of patient-reported symptoms. This is accompanied by greater harm of major extent in the overall rate of severe AEs (CTCAE grade ≥ 3). The negative effect does not call into question the advantages of the symptom outcomes, but, in the overall consideration, leads to a downgrading of the extent of the added benefit. Further

[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].

individual outcomes of the category of non-serious/non-severe side effects show partly greater and partly lesser harm.

In summary, there is a hint of considerable added benefit of upadacitinib in comparison with the ACT dupilumab for women with moderate to severe atopic dermatitis who are candidates for systemic therapy.

Men

The positive effects, each with major extent, for the symptom outcomes of remission and itching are decisive for the conclusion on the added benefit for men. There is another positive effect with considerable extent for the outcome of patient-reported symptoms. Individual outcomes of the category of non-serious/non-severe side effects show partly greater and partly lesser harm.

In summary, there is a hint of major added benefit of upadacitinib in comparison with the ACT dupilumab for men with moderate to severe atopic dermatitis who are candidates for systemic therapy.

Subquestion 2: adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy

An added benefit is not proven because the company did not present any suitable data for the assessment of the added benefit of upadacitinib in comparison with the ACT dupilumab for adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy.

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

Table 3: Upadacitinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy[b]	Dupilumab (possibly in combination with TCS and/or TCI)	Adults for whom 30 mg is the appropriate dose: ▪ Women: hint of considerable added benefit ▪ Men: hint of major added benefit
		Adults for whom 15 mg is the appropriate dose: added benefit not proven
		Adolescents (12-17 years)[c]: added benefit not proven
a. Presented is the ACT specified by the G-BA. b. According to the approval, the therapeutic indication comprises those patients who are candidates for systemic therapy. For the determination of the ACT, adults and adolescents 12 years and older with moderate to severe atopic dermatitis are considered for whom long-term/continuous systemic therapy is indicated, as the drug upadacitinib is to be used as continuous therapy and is therefore only an option for patients for whom long-term/continuous systemic therapy is indicated. c. Only a dose of 15 mg upadacitinib is approved for adolescents (12-17 years). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TCI: topical calcineurin inhibitors; TCS: topical glucocorticoids		

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

2.2 Research question

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

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

Table 4: Research question of the benefit assessment of upadacitinib

Therapeutic indication	**ACT[a]**
Moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy[b]	Dupilumab (possibly in combination with TCS and/or TCI)
a. Presentation of the ACT specified by the G-BA. b. According to the approval, the therapeutic indication comprises those patients who are candidates for systemic therapy. For the determination of the ACT, adults and adolescents 12 years and older with moderate to severe atopic dermatitis are considered for whom long-term/continuous systemic therapy is indicated, as the drug upadacitinib is to be used as continuous therapy and is therefore only an option for patients for whom long-term/continuous systemic therapy is indicated. 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 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 upadacitinib (status: 24 June 2021)
- bibliographical literature search on upadacitinib (last search on 1 July 2021)
- search in trial registries/trial results databases for studies on upadacitinib (last search on 6 July 2021)
- search on the G-BA website for upadacitinib (last search on 6 July 2021)

To check the completeness of the study pool:

- search in trial registries for studies on upadacitinib (last search on 8 September 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: upadacitinib vs. 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 [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
M16-046 (Heads Up[c])	No	Yes	No	Yes [3]	Yes [4,5]	Yes [6]

a. Study for which the company was sponsor.
b. References of study registry entries and any available reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.
CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool for the benefit assessment of upadacitinib consists of the RCT M16-046 (hereinafter referred to as "Heads Up" study). This study included only adults with moderate to severe atopic dermatitis. There are no data corresponding to the research question of the present benefit assessment on adolescents 12 years and older who are also comprised by the therapeutic indication.

The study pool concurs with that of the company, which additionally presented supplementary analyses on adolescents 12 years and older from the 3 pivotal approval studies M16-045 (hereinafter referred to as "Measure Up 1" study) [7,8], M18-891 (hereinafter referred to as "Measure Up 2" study) [8,9] and M16-047 (hereinafter referred to as "AD Up" study) [10,11] and used these analyses to transfer the results of the Heads Up study from adults to adolescents. In the present data constellation, an evidence transfer to adolescent patients is not possible, however. This is explained in Section 2.5.

In the following, adults and adolescents 12 years and older are addressed in separate research subquestions:

- Subquestion 1: adults with moderate to severe atopic dermatitis who are candidates for systemic therapy
- Subquestion 2: adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy

2.4 Subquestion 1: adults with moderate to severe atopic dermatitis who are candidates for systemic therapy

2.4.1 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: upadacitinib vs. dupilumab

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Heads Up	RCT, double-blind, parallel	Adults (≥ 18 years to ≤ 75 years) with moderate to severe atopic dermatitis[b, c] who are candidates for systemic therapy[d]	Upadacitinib (N = 348) Dupilumab (N = 344)	Screening: 35 days Treatment: 24 weeks Follow-up: up to 12 weeks[e]	129 centres in: Australia, Canada, Croatia, Czech Republic, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Malaysia, Netherlands, New Zealand, Norway, Poland, Singapore, Spain, Taiwan, Ukraine, United Kingdom, United States 2/2019–12/2020[f]	Primary: EASI 75 at week 16 Secondary: morbidity, AEs

a. Primary outcomes include information without consideration of relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Chronic AD with onset of symptoms at least 3 years prior to baseline, and meeting Hanifin and Rajka criteria [12].
c. According to the inclusion criteria, patients had to fulfil the following criteria: at screening and baseline, EASI ≥ 16, vIGA-AD ≥ 3, ≥ 10% BSA of AD involvement; baseline weekly average of WP-NRS ≥ 4 (calculated from the 7 consecutive days immediately preceding the baseline visit; a minimum of 4 daily scores out of the 7 days is needed).
d. According to the inclusion criteria, patients had to fulfil one of the following criteria: documented history (within 6 months of the baseline visit) of inadequate response to TCS or TCI or documented systemic therapy for AD within 6 months prior to the baseline visit or topical treatment otherwise inadvisable (e.g., because of important side effects or safety risks).
e. Only for patients who did not participate in an open-label extension study with 30 mg upadacitinib for another 52 weeks immediately afterwards.
f. Dates of analysis: final analysis on efficacy outcomes on 21 October 2020, after all patients had reached week 24; final analysis on side effect outcomes at the end of the study on 28 December 2020, according to Module 4 A.

AD: atopic dermatitis; AE: adverse event; BSA: body surface area; EASI: Eczema Area and Severity Index; N: number of randomized patients; RCT: randomized controlled trial; TCI: topical calcineurin inhibitors; TCS: topical glucocorticoids; vIGA-AD: validated Investigator Global Assessment for Atopic Dermatitis; WP-NRS: Worst Pruritus Numerical Rating Scale

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

Study	Intervention	Comparison
Heads Up	Upadacitinib 30 mg/day orally[a]	Dupilumab 600 mg SC on day 1, then 300 mg SC every 2 weeks until week 22[b]
	Background therapy ▪ emollients[c] twice daily for at least 7 days before baseline and during the entire treatment duration **Adjustment of study treatment** ▪ no dose adjustment allowed ▪ in case of emergency surgery, treatment interruption is allowed until the surgical site has healed **Non-permitted pretreatment** ▪ topical TCS and TCI within 7 days before baseline ▪ systemic therapy (e.g. with glucocorticoids or ciclosporin) and phototherapy within 4 weeks before baseline ▪ JAK inhibitors ▪ dupilumab ▪ biologics within 12 weeks or 5 half-lives before baseline ▪ live vaccines within 4 weeks before baseline **Permitted concomitant treatment** ▪ topical treatments (e.g. TCS or TCI) if considered necessary by the investigator ("topical rescue therapy")[d] ▪ topical therapy with anti-infectives, antihistamines, and bleach baths may be used in the first 16 weeks of treatment if they were used for reasons other than AD and in the 6 months prior to the screening visit **Non-permitted concomitant treatment** ▪ systemic therapies (e.g. glucocorticoids[e], methotrexate, ciclosporin, azathioprine, PDE4 inhibitors, mycophenolate mofetil), prescription emollients, emollients containing additives[c], or phototherapy for the treatment of AD[f] ▪ JAK inhibitors ▪ biologics (e.g. abatacept, ixekizumab) ▪ strong CYP3A inhibitors or inducers ▪ live vaccines	

a. To maintain blinding, dupilumab placebo SC was injected on day 1 and every 2 weeks.
b. To maintain blinding, oral upadacitinib placebo was administered daily.
c. Emollients with additives (e.g. ceramide, urea) were only allowed if they were initiated before baseline.
d. If there was no response to topical therapy within 7 days, systemic therapies and phototherapies were to be used at the investigator's discretion.
e. With the exception of inhaled, nasal and ophthalmic glucocorticoids as well as oral glucocorticoids as rescue therapy.
f. After a lack of response to topical therapies, initiation of these therapies was possible as another "rescue therapy" at the discretion of the investigator, but led to permanent discontinuation of the study medication.

AD: atopic dermatitis; CYP3A: cytochrome P450 3A; JAK: Janus kinase; PDE4: phosphodiesterase type 4; RCT: randomized controlled trial; SC: subcutaneous; TCI: topical calcineurin inhibitors; TCS: topical corticosteroids

Study design

Study design, patient population and interventions

The Heads Up study is a randomized, double-blind RCT comparing upadacitinib with dupilumab. The treatment duration was 24 weeks. Subsequently, patients had the opportunity to participate in an open-label, single-arm extension study with 30 mg upadacitinib.

The Heads Up study investigated adults aged 18 to 75 years who had chronic atopic dermatitis for at least 3 years. Disease severity was defined based on the following criteria: vIGA-AD ≥ 3, EASI ≥ 16, ≥ 10% body surface area involvement, and itching with a weekly average of WP-NRS ≥ 4 calculated from the 7 consecutive days before randomization (a minimum of 4 daily scores out of the 7 days was needed). For the present benefit assessment, the severity definition based on vIGA-AD, EASI and body surface area involvement is considered to be a sufficient representation of moderate to severe atopic dermatitis.

Patients had to have a history of inadequate response to topical treatment with TCS and TCI or to systemic therapy within 6 months prior to randomization, or topical treatments were otherwise medically inadvisable (e.g. because of side effects). It is not clear from the available information how an inadequate response to topical or systemic therapy was defined.

Patients were randomly assigned to the study arms. Stratification factors were age (< 40 years, ≥ 40 to < 65 years, ≥ 65 years) and disease severity (vIGA-AD 3, vIGA-AD 4). 348 patients were randomly allocated to the upadacitinib arm and 344 patients to the dupilumab arm.

Patients in the intervention arm received 30 mg upadacitinib daily. This dosage is approved in the therapeutic indication [13]. In the comparator arm, dupilumab was administered in compliance with the SPC [14]. If the EASI worsened by ≥ 25% compared with baseline at 2 consecutive visits after week 4, treatment with the study medication had to be permanently discontinued.

Primary outcome of the study was the EASI 75. Patient-relevant outcomes on morbidity and side effects were additionally recorded. Outcomes from the category of health-related quality of life were not recorded.

Background therapy and rescue therapy

No later than 7 days before the first administration of the study medication and during the entire treatment duration, all patients had to use emollients at least twice daily as background therapy.

Topical TCS and/or TCI therapy had to be discontinued no later than 7 days before baseline. At the start of treatment, patients in both study arms thus received monotherapy with upadacitinib or dupilumab. However, both drugs are approved both as monotherapy and in combination with TCS and/or TCI [13,14]. It can be assumed that in everyday clinical practice, ongoing topical therapy would be reduced and phased out only upon improvement. This was not mandated in the Heads Up study. It is unclear whether additional topical therapy would

have been indicated for some of the patients at baseline. However, treatment escalation (referred to as "rescue therapy" by the company) could be provided in the course of the study if this was deemed necessary by the investigator; if possible initially with topical treatments such as TCS and/or TCI. Study medication was continued in these cases. In the Heads Up study, 24% of the patients received topical rescue therapy both in the upadacitinib arm and in the dupilumab arm. It is not clear from the available information whether, and if so, according to which criteria, topical therapies were discontinued again in the course of the study.

Patients who did not respond adequately within 7 days of topical treatment were to receive systemic therapy and phototherapy at the discretion of the investigator. This led to permanent discontinuation of the study medication, however. Only few patients received systemic therapy (4% in the upadacitinib arm and 1% in the dupilumab arm).

Suitability of the patients for systemic therapy

The update "Systemic therapy for atopic dermatitis" of the German guideline for atopic dermatitis [15] contains the checklist "Therapeutic indication for anti-inflammatory systemic therapy in adults". According to this checklist, patients are suitable for systemic therapy if there is both a relevant objective severity grade (e.g. determined based on the EASI score > 15 or on > 10% body surface area involvement), a relevant subjective burden (based on the Dermatology Life Quality Index [DLQI] questionnaire on health-related quality of life [DLQI > 10], itching [> 6 on a visual analogue scale or numeric rating scale from 0 to 10] or relevant night-time sleep disturbances due to itching/eczema), and a lack of response to therapy. The European guideline, on the other hand, does not call for stringent subjective criteria regarding the therapeutic indication for systemic therapy [16,17].

The relevant objective severity grade and the lack of response to therapy are already fulfilled by the inclusion criteria of the Heads Up study, since an EASI score ≥ 16 had to be present at baseline and patients had to have a history of inadequate response to topical treatment with TCS and TCI or to systemic therapy for inclusion in the study, or topical treatments were otherwise medically inadvisable (see above). There is no definition of inadequate response to topical treatment. The criterion of relevant subjective burden was fulfilled in just over 80% of the patients based on a baseline WP-NRS score ≥ 6 (see also Table 8).

In summary, it is therefore assumed that continuous systemic therapy is an option for the study population in the Heads Up study.

Upadacitinib dosage used in the Heads Up study

Approval according to the SPC

According to the SPC [13], the recommended dose of upadacitinib for patients aged 65 years and older is 15 mg daily. For patients aged 18 to 64 years, daily doses of 15 mg or 30 mg are available based on individual patient presentation. A dose of 30 mg daily may be appropriate for patients with high disease burden and an inadequate response to 15 mg. The lowest effective dose for maintenance should be considered. Thus, for patients aged 18 to 64 years, there is no

specific guidance in the SPC as to when the 15 mg or 30 mg doses of upadacitinib should be administered. However, it can be assumed that the 30 mg dose is more likely to be administered in severe atopic dermatitis than in moderate atopic dermatitis.

Only the 30 mg dose was used in the Heads Up study

According to the inclusion criteria, the Heads Up study included patients aged 18 to 75 years with moderate to severe atopic dermatitis. As described above, all patients in the Heads Up study, regardless of age, received upadacitinib exclusively in the 30 mg dose. This meant that it was neither possible to start treatment with the also approved dose of 15 mg nor was it permitted to adjust the dose to 15 mg during the course of the study; and such an adjustment did not take place.

As described above, only the 15 mg dose should be used in patients aged 65 years and older, according to the SPC [13]. Thus, patients aged ≥ 65 years in the Heads Up study did not receive the approval-compliant dose for this age group because they also received the 30 mg dose. However, since only a small proportion of the study population (5%) in the Heads Up study was ≥ 65 years of age, this deviation from the SPC has no impact on the present assessment.

According to the SPC, both the 15 mg and the 30 mg dose can be used in patients aged between 18 and 64 years [13]. Since it is assumed that the 30 mg dose of upadacitinib is more likely to be administered in the presence of severe atopic dermatitis (see above), it was checked whether most patients included had severe disease at baseline. Based on the classification of severity grades according to EASI [18], the Institute's calculations based on mean values and standard deviations, assuming a normal distribution in the study population, severe disease was predominant (about 77%). According to the classification of severity grades based on vIGA-AD [19], moderate (vIGA-AD = 3) and severe (vIGA-AD = 4) disease severity was represented in approximately equal proportions in both treatment groups.

In summary, it is assumed that a dose of 30 mg at baseline was appropriate for the majority of the study population. However, due to the uncertainty and the fact that no dose adjustment to the lower dose (15 mg) was allowed during the course of the study in case of response to treatment with upadacitinib, the certainty of conclusions is reduced. Thus, at most hints, e.g. of an added benefit, can be derived for all outcomes on the basis of the effects shown in the Heads Up study.

Conclusion on added benefit is only possible for patients for whom 30 mg is the appropriate dose

As described above, all patients in the intervention arm of the Heads Up study received upadacitinib at a dose of 30 mg, and it is assumed that 30 mg was the correct dose for the majority of patients, at least at the start of the study. No results are available in comparison with the ACT dupilumab for adult patients for whom 15 mg is the appropriate dose.

The approval studies Measure Up 1, Measure Up 2 and AD Up compared the 15 mg and 30 mg doses of upadacitinib against placebo for 16 weeks (see also Section 2.5). This allows a comparison of the results of the 15 mg and the 30 mg doses of upadacitinib for adults over a treatment period of 16 weeks. Table 21 in Appendix B of the full dossier assessment shows the responder rates for the different operationalizations of the EASI (EASI 100, EASI 90, EASI 75) as well as for improvement of itching to 0 or 1, or responder analyses for an improvement by ≥ 4 points, recorded with the WP-NRS. Here, the proportion of patients with a treatment response under the 30 mg dose is mostly ≥ 10% higher than under the 15 mg dose. When considering the total populations of the studies Measure Up 1, Measure Up 2 and AD Up, the European Medicines Agency (EMA) also points out in the European Public Assessment Report (EPAR) that there is a dose dependence with differences in responder rates between 10 and 19 percentage points, and that, in post-hoc analyses of the studies Measure Up 1 and Measure Up 2, the confidence intervals of the efficacy outcomes of both doses do not overlap for almost all outcomes [20].

As the response rates in the different outcome operationalizations differ between patients who received 15 mg and those who received 30 mg, and there are also no ceiling effects, it can be assumed, based on the observed differences, that the effects under treatment with upadacitinib in the 15 mg dose become smaller or absent when compared with the ACT dupilumab than in a 30 mg dose.

In the present data situation, a conclusion on the added benefit is therefore only drawn for patients for whom 30 mg is the appropriate dose.

In Module 4 A, the company did not comment on the impact the dose of upadacitinib used in the study has on the benefit assessment.

Dates of analysis

In Module 4 A, the company provided the following dates of analysis for the completed Heads Up study:

- First analysis date (21 October 2020): primary analysis; analysis after all patients had reached week 24; only and final analysis of efficacy outcomes
- Second analysis date (28 December 2020): end of study, referred to by the company as "final data cut-off"; analysis of side effect outcomes after all patients had either entered the extension study after week 24 or had had the follow-up visit 12 weeks after the end of the last dupilumab injection (see Section 2.4.2.2)

Both dates of analysis were prespecified.

Patient characteristics

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

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

Study Characteristic Category	Upadacitinib N[a] = 348	Dupilumab N[a] = 344
Heads Up		
Age [years], mean (SD)	37 (15)	37 (14)
Age group, n (%)		
< 40 years	228 (66)	226 (66)
40 – < 65 years	102 (29)	101 (29)
≥ 65 years	18 (5)	17 (5)
Sex [F/M], %	47/53	44/56
Region, n (%)		
US/Puerto Rico/Canada	140 (40)	131 (38)
Other	208 (60)	213 (62)
Family origin n (%)		
White	235 (68)	244 (71)
Black or African American	25 (7)	15 (4)
Asian	77 (22)	78 (23)
Other	11 (3)	7 (2)
EASI		
Mean (SD)	30.8 (12.5)	28.8 (11.5)
Median [Q1; Q3]	27.3 [20.6; 38.0]	25.5 [19.8; 34.5]
BSA (%)		
Mean (SD)	48.2 (24.0)	44.4 (22.8)
Median [Q1; Q3]	42 [29.0; 70.0]	40 [25.5; 60.0]
vIGA-AD, n (%)		
3 (moderate)	174 (50)	171 (50)
4 (severe)	174 (50)	173 (50)
WP-NRS[b]		
Mean (SD)	7.4 (1.6)	7.5 (1.7)
Median [Q1; Q3]	7.5 [6.6; 8.5]	7.7 [6.4; 8.7]
NRS ≤ 6, n (%)	64 (18)	66 (19)
NRS > 6, n (%)	282 (82)	276 (81)
HN-PGIS		
Mean (SD)	3.8 (1.6)	4.0 (1.5)
Median [Q1; Q3]	4.0 [3.0; 5.0]	4.0 [3.0; 5.0]
Disease duration: time between first diagnosis and first dose of study medication [years], mean (SD)	23.5 (14.7)	25.1 (14.8)
Treatment discontinuation[c, d], n (%)	32 (9)	25 (7)
Study discontinuation[e], n (%)	30 (9)	24 (7)

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

Study Characteristic Category	Upadacitinib N[a] = 348	Dupilumab N[a] = 344
a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant. b. Data refer to the weekly average. c. For patients receiving systemic rescue therapy, the primary reason for discontinuation of the study medication did not necessarily have to be the systemic rescue therapy. d. Reasons for treatment discontinuation in the intervention vs. control arm were: AEs (10 vs. 4 patients), patient request (8 vs. 6 patients), lost to follow-up (4 vs. 5 patients), lack of efficacy (6 vs. 3 patients), logistic restrictions due to COVID-19 (1 vs. 2 patients), other (3 vs. 5 patients). e. Reasons for study discontinuation in the intervention vs. control arm were: AEs (7 vs. 3 patients), patient request (11 vs. 8 patients), lost to follow-up (5 vs. 8 patients), logistic restrictions due to COVID-19 (1 vs. 1 patient), other (6 vs. 4 patients). AD: atopic dermatitis; AE: adverse event; BSA: body surface area; COVID-19: coronavirus disease 2019; EASI: Eczema Area and Severity Index; F: female; HN-PGIS: Head and Neck-Patient Global Impression of Severity; M: male; n: number of patients in the category, N: number of randomized patients; NRS: numeric rating scale; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; vIGA-AD: validated Investigator Global Assessment for Atopic Dermatitis; WP-NRS: Worst Pruritus Numerical Rating Scale		

Patient characteristics were sufficiently balanced between both treatment groups.

In both study arms, the mean age of the patients was about 37 years, and most were of white family origin. Men and women were represented in roughly equal proportions. The mean disease duration of the atopic dermatitis was about 24 years.

According to the classification of the severity grades based on EASI [18], most of the included patients had severe disease. According to the classification of severity grades based on vIGA-AD, moderate and severe disease severity was represented in approximately equal proportions in both treatment groups. The vast majority of patients rated their itching at baseline on the WP-NRS as > 6 in both treatment groups.

The proportion of treatment and study discontinuations was below 10% in both treatment arms.

Table 9 shows the prior therapies of the patients in the Heads Up study.

Table 9: Characteristics of the study population (prior therapy[a]) – RCT, direct comparison: upadacitinib vs. dupilumab

Study Characteristic Category	Upadacitinib N = 348	Dupilumab N = 344
Heads Up		
Any prior therapy of atopic dermatitis	348 (100)	343 (99.7)
Prior topical therapy, n (%)	334 (96)	327 (95)
TCS	322 (93)	313 (91)
High-potency TCS	237 (68)	240 (70)
Moderate-potency TCS	169 (49)	136 (40)
Low-potency TCS	115 (33)	111 (32)
TCI	114 (33)	130 (38)
Other	47 (14)	47 (14)
Prior systemic therapy, n (%)	180 (52)	175 (51)
Prior biologic systemic therapy	8 (2)	2 (1)
Prior non-biologic immunomodulatory systemic therapy	177 (51)	175 (51)
Other	129 (37)	111 (32)
Phototherapy, n (%)	60 (17)	57 (17)
Other	88 (25)	86 (25)

a. It is unclear whether the data refer to the last 6 months before study inclusion or to any prior therapies.

n: number of patients in the category, N: number of randomized patients; RCT: randomized controlled trial; TCI: topical calcineurin inhibitors; TCS: topical glucocorticoids

Regarding the administered prior therapies, the treatment arms of the Heads Up study were balanced. It is not clear from the available information whether the information on prior therapies refer to the last 6 months before study inclusion, as required by the inclusion criteria, or to any prior therapies.

92% of the patients included had received TCS, about 70% had received high-potency TCS. At around 4%, only a very small proportion of the included patients had not received any prior topical therapy for the treatment of atopic dermatitis. About half of the patients had been treated with systemic therapy. The main treatments used here were non-biologic immunomodulatory therapies.

About 95% of the patients had shown an insufficient response or a loss of efficacy to prior therapies, but it is unclear how the insufficient response was defined in the Heads Up study.

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: upadacitinib vs. dupilumab

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
Heads Up	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the Heads Up study is rated as low.

Transferability of the study results to the German health care context

The company described for the Heads Up study that the patients included correspond to the target population and that the treatment with upadacitinib was carried out in compliance with the SPC. To assess transferability, the company also compared the patient characteristics of age, proportion of women, disease duration, comorbidities (≥ 1 comorbidity, allergic rhinitis, asthma) in the Heads Up study with published characteristics of adult German patients with atopic dermatitis from 2 non-interventional studies [21,22]. From the point of view of the company, the mean age and the long disease duration at the time of study inclusion with typical disease onset in childhood correspond to the actual health care setting. According to the company, the proportion of women is also within the range published in the 2 non-interventional studies.

For the studies Measure Up 1, Measure Up 2 and AD Up, the company described that the included patients aged between 12 and 75 years are also comprised by the therapeutic indication of upadacitinib and were treated in compliance with the SPC. Besides, the included adolescents were mostly white and had had the disease for several years on average.

Overall, in the opinion of the company, there are no indications that the study populations and study results are not transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality

- all-cause mortality

- Morbidity
  - symptoms – remission (recorded with the EASI 100)
  - symptoms – itching (recorded with the WP-NRS)
  - patient-reported symptoms (recorded with the HN-PGIS)
- Health-related quality of life
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - infections (SOC “infections and infestations”, AE)
  - serious infections (SOC “infections and infestations”, SAE)
  - conjunctivitis (Preferred Term [PT], AE)
  - eye disorders (SOC, AE)
  - further specific AEs, if any

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

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

Table 11: Matrix of outcomes – RCT, direct comparison: upadacitinib vs. dupilumab

Study	Outcomes												
	All-cause mortality	Symptoms – remission (EASI 100)	Symptoms – itching (WP-NRS)	Patient-reported symptoms (HN-PGIS)	Health-related quality of life	SAEs[a]	Severe AEs[a, b]	Discontinuation due to AEs	Infections[c]	Serious infections[c]	Conjunctivitis (PT, AE)	Eye disorders (SOC, AE)	Acne (PT, AE)
Heads Up	Yes	Yes	Yes	Yes	No[d]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Without the PT atopic dermatitis.
b. Operationalized as CTCAE grade ≥ 3.
d. All AEs of the MedDRA SOC "infections and infestations" are used for the recording of infections, and all SAEs for the recording of serious infections.
d. Outcome not recorded.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EASI: Eczema Area and Severity Index; HN-PGIS: Head and Neck-Patient Global Impression of Severity; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; WP-NRS: Worst Pruritus Numerical Rating Scale

Notes on outcomes

Symptoms – EASI

The EASI is an instrument used for the objective assessment of atopic dermatitis severity [23-25]. The physician rates the symptoms on a symptom score between 0 (no symptoms) and 3 (severe symptoms) and also estimates the proportion of body surface area involvement as a percentage of the total body surface. With different weighting of the various values, a total score is calculated from this, which can reach values between 0 and 72. Higher values indicate greater disease severity.

The present assessment uses the EASI 100. EASI 100 indicates complete remission of the external signs of dermatitis (i.e. 100% from baseline). EASI 90 and EASI 75 (90% and 75% reduction of the baseline EASI score [response]) are presented as additional information.

Symptoms – itching (WP-NRS)

The WP-NRS is a self-reported instrument to determine the worst itching within the last 24 hours. Recording is done using a numerical scale from 0 (no itching) to 10 (worst imaginable itching). In the Heads Up study, recording of itching with the WP-NRS was conducted daily up to week 16 via an electronic patient diary, which was given to the patients after the screening. Afterwards, the WP-NRS was also recorded electronically at the scheduled study visits (every

2 weeks until week 24). The weekly mean of the WP-NRS was included in the analyses of the company up to week 16.

The present benefit assessment uses the operationalization of WP-NRS = 0 at week 24. This means no symptom of itching. In addition, the prespecified responder analysis for the improvement by ≥ 4 points at week 24 compared with baseline is presented as supplementary information, as this response criterion is also considered an important outcome for patients who cannot achieve complete absence of symptoms. The response criterion corresponds to ≥ 15% of the scale range and, as explained in the *General Methods* of the Institute [1,26], reflects with sufficient certainty a change noticeable for the patient.

Patient-reported symptoms (HN-PGIS)

The HN-PGIS is a patient-reported measurement tool to assess the severity of symptoms of atopic dermatitis in the head and neck area on a scale from 0 (no symptoms) to 6 (cannot be ignored and markedly limits my daily activities). Higher values are associated with more severe symptoms and greater limitations for patients.

The HN-PGIS is patient-relevant. Lesions in the head and neck area can be perceived by the affected person as particularly disturbing because they are difficult to hide [27,28]. In principle, however, it would also be desirable to assess symptom severity of the patients in relation to the whole body, as other parts of the body, such as the hands and insides of elbows and knees, can also be affected in adults [28,29].

The present benefit assessment uses the proportion of patients with an HN PGIS of 0 at week 24.

Notes on types of analysis

For the main analysis of the binary outcomes on morbidity, also referred to by the company as "modified NRI-C analysis", the company used responder analyses at week 24 in Module 4 A using modified non-responder imputation (NRI) with multiple imputation (MI) to impute missing values. In this imputation strategy, missing data due to coronavirus disease 2019 (COVID-19) are imputed using MI. Patients with missing values that were not due to COVID-19 and patients who received systemic therapy or phototherapy as rescue therapy were rated as non-responders. This approach is appropriate because initiation of systemic therapy or phototherapy led to permanent treatment discontinuation. Patients who received topical "rescue therapy" (to be understood as a change in background therapy) had their actual values included in the analysis. The analyses were based on a generalized linear model (GLM) with treatment and the prespecified main stratification factor of vIGA-AD as covariables. The present benefit assessment uses this main analysis of the company.

As supplementary information, the company presented results of sensitivity analyses with a modified imputation strategy, in which missing values that did not occur due to COVID-19 –

in contrast to the primary analysis – were imputed with an MI and not by means of NRI. The presented sensitivity analyses overall show results that are consistent with the main analysis.

2.4.2.2 Risk of bias

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

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – direct comparison: upadacitinib vs. dupilumab

Study		Outcomes												
	Study level	All-cause mortality	Symptoms – remission (EASI 100)	Symptoms – itching (WP-NRS)	Patient-reported symptoms (HN-PGIS)	Health-related quality of life	SAEs	Severe AEs[a]	Discontinuation due to AEs	Infections[b]	Serious infections[b]	Conjunctivitis (PT, AE)	Eye disorders (SOC, AE)	Acne (PT, AE)
Heads Up	L	L	L	L	L	–[c]	H[d]	H[d]	H[d]	H[d]	H[d]	H[d]	H[d]	H[d]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. All AEs of the MedDRA SOC "infections and infestations" are used for the recording of infections, and all SAEs for the recording of serious infections.
c. Outcome not recorded.
d. Differences in observation periods between the arms.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EASI: Eczema Area and Severity Index; H: high; HN-PGIS: Head and Neck-Patient Global Impression of Severity; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; WP-NRS: Worst Pruritus Numerical Rating Scale

The risk of bias of the results of the outcomes of all-cause mortality, remission (EASI 100) and itching (WP-NRS), as well as of patient-reported symptoms (HN-PGIS) is rated as low.

The risk of bias of the results for all outcomes of the category of side effects is rated as high. This is due to different observation durations between the study arms. The planned duration of follow-up observation was 30 days in the upadacitinib arm and 84 days in the dupilumab arm. In addition, the final analysis date for side effects basically depended on whether or not the patients switched to the extension study after the end of the Heads Up study (see Section 2.4.1). Patients who participated in the extension study after the Heads Up study were to have their final visit after the 24-week treatment period. All other patients were to have their final visit 12 weeks after their last injection. The last injection took place after treatment week 22. About 70% of the patients from both treatment arms switched to the extension study and therefore should have been included in the final visit after 24 weeks of study duration. It is unclear whether the planned follow-up observation period was included in the analysis.

The actual mean observation period was about 27 weeks for the upadacitinib arm and about 33 weeks for the dupilumab arm.

2.4.2.3 Results

Table 13 summarizes the results of the comparison of upadacitinib with dupilumab in adults with moderate to severe atopic dermatitis who are candidates for systemic therapy. Where necessary, calculations conducted by the Institute 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 13: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: upadacitinib vs. dupilumab (multipage table)

Study Outcome category Outcome	Upadacitinib		Dupilumab		Upadacitinib vs. dupilumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Heads Up					
Mortality					
All-cause mortality[b]	348	1 (0.3)	344	0 (0)	2.97 [0.12; 72.55]; 0.505
Morbidity					
Symptoms					
EASI 100 (remission)	348	100 (28.7)	344	48 (14.0)	2.05 [1.50; 2.79]; < 0.001
EASI 90 (supplementary information)	*348*	*227 (65.3)*	*344*	*197 (57.3)*	*1.14 [1.01; 1.28]; 0.034*
EASI 75 (supplementary information)	*348*	*277 (79.6)*	*344*	*263 (76.4)*	*1.04 [0.96; 1.13]; 0.303*
Itching (WP-NRS 0)	348	92 (26.4)	344	29 (8.4)	3.14 [2.12; 4.63]; < 0.001
Itching (WP-NRS, improvement by ≥ 4 points) (supplementary information)	*348*	*212 (60.8)*	*344*	*178 (51.7)*	*1.18 [1.03; 1.34]; 0.017*
Patient-reported symptoms (HN-PGIS 0)	348	99 (28.5)	344	58 (16.9)	1.69 [1.27; 2.26]; < 0.001
Health-related quality of life	Not recorded				
Side effects[c]					
AEs (supplementary information)[d]	348	269 (77.3)	344	227 (66.0)	–
SAEs[d]	348	13 (3.7)	344	7 (2.0)	1.84 [0.74; 4.55]; 0.189[e]
Severe AEs[d, f]	348	29 (8.3)	344	13 (3.8)	2.21 [1.17; 4.17]; 0.015
Discontinuation due to AEs	348	11 (3.2)	344	4 (1.2)	2.72 [0.87; 8.45]; 0.084
Infections (SOC, AE)[g]	348	161 (46.3)	344	133 (38.7)	1.20 [1.00; 1.43]; 0.044
Serious infections (SOC, SAE)[g]	348	4 (1.1)	344	2 (0.6)	1.98 [0.36; 10.72]; 0.533[h]
Conjunctivitis (PT, AE)	348	5 (1.4)	344	35 (10.2)	0.14 [0.06; 0.36]; < 0.001
Eye disorders (SOC, AE)	348	26 (7.5)	344	49 (14.2)	0.52 [0.33; 0.82]; 0.005
Acne (PT, AE)	348	64 (18.4)	344	11 (3.2)	5.75 [3.09; 10.71]; < 0.001

Table 13: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: upadacitinib vs. dupilumab (multipage table)

Study Outcome category Outcome	Upadacitinib N	Upadacitinib Patients with event n (%)	Dupilumab N	Dupilumab Patients with event n (%)	Upadacitinib vs. dupilumab RR [95% CI]; p-value[a]
a. Unless stated otherwise: GLM (log-link), treatment and vIGA-AD as covariables. b. Deaths were recorded within the framework of the AEs. c. GLM with treatment as covariable. d. Without the PT atopic dermatitis. e. Normal distribution approximation, Wald test. f. Operationalized as CTCAE grade ≥ 3. g. All AEs of the MedDRA SOC "infections and infestations" are used for the recording of infections, and all SAEs for the recording of serious infections. h. Institute's calculation, RR [95% CI] (asymptotic) and p-value (unconditional exact test, CSZ method according to [30]). AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; EASI: Eczema Area and Severity Index; GLM: generalized linear model; HN-PGIS: Head and Neck-Patient Global Impression of Severity; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vIGA-AD: validated Investigator Global Assessment for Atopic Dermatitis; WP-NRS: Worst Pruritus Numerical Rating Scale					

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section 2.4.1).

Mortality

All-cause mortality

For the outcome of all-cause mortality, one death occurred in the upadacitinib arm. No statistically significant difference was shown between upadacitinib and dupilumab. This results in no hint of an added benefit of upadacitinib in comparison with dupilumab; an added benefit is therefore not proven.

Morbidity

Symptoms – remission (EASI 100)

A statistically significant difference in favour of upadacitinib in comparison with dupilumab was shown for the outcome of symptoms – remission (EASI 100). This results in a hint of an added benefit of upadacitinib in comparison with dupilumab.

Symptoms – itching (WP-NRS 0)

A statistically significant difference in favour of upadacitinib in comparison with dupilumab was shown for the outcome of symptoms – itching (WP-NRS 0). This results in a hint of an added benefit of upadacitinib in comparison with dupilumab.

Symptoms – patient-reported symptoms (HN-PGIS 0)

A statistically significant difference in favour of upadacitinib in comparison with dupilumab was shown for the outcome of patient-reported symptoms (HN-PGIS 0). This results in a hint of an added benefit of upadacitinib in comparison with dupilumab.

Health-related quality of life

No outcomes in the outcome category of health-related quality of life were recorded in the Heads Up study. This results in no hint of an added benefit of upadacitinib in comparison with dupilumab in this outcome category; an added benefit is therefore not proven.

Side effects

Overall rates of SAEs and discontinuation due to AEs

No statistically significant difference between upadacitinib and dupilumab was shown for the outcomes of SAEs and discontinuation due to AEs. This results in no hint of greater or lesser harm from upadacitinib in each case; greater or lesser harm is therefore not proven.

Overall rates of severe AEs (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of upadacitinib in comparison with dupilumab was shown for the outcome of severe AEs. However, there is an effect modification by the characteristic of sex. For women, this results in a hint of greater harm from upadacitinib in comparison with dupilumab. For men, there is no hint of greater or lesser harm from upadacitinib in each case; greater or lesser harm for men is therefore not proven for this outcome (see Section 2.4.2.4).

Infections

The present benefit assessment uses the outcome of infections via the AEs that occurred in the SOC “infections and infestations”.

A statistically significant difference to the disadvantage of upadacitinib in comparison with dupilumab was shown for the outcome of infections. However, there is an effect modification by the characteristic of age. For patients ≥ 40 years of age, this results in a hint of greater harm from upadacitinib in comparison with dupilumab for the outcome of infections. For patients < 40 years of age, there is no hint of greater or lesser harm from upadacitinib; greater or lesser harm is therefore not proven for patients < 40 years of age for this outcome (see Section 2.4.2.4).

Serious infections

The present benefit assessment uses the outcome of infections via the SAEs that occurred in the SOC “infections and infestations”.

No statistically significant difference between upadacitinib and dupilumab was shown for the outcome of serious infections. This results in no hint of greater or lesser harm from upadacitinib; greater or lesser harm is therefore not proven.

Conjunctivitis (PT, AE)

A statistically significant difference in favour of upadacitinib in comparison with dupilumab was shown for the outcome of conjunctivitis (SOC, AE). This results in a hint of lesser harm from upadacitinib in comparison with dupilumab.

Eye disorders (SOC, AE)

A statistically significant difference in favour of upadacitinib in comparison with dupilumab was shown for the outcome of eye disorders (SOC, AE). However, there is an effect modification by the characteristic of disease severity. For patients with a vIGA-AD 4, this results in a hint of lesser harm from upadacitinib in comparison with dupilumab. For patients with a vIGA-AD 3, there is no hint of greater or lesser harm from upadacitinib; greater or lesser harm is therefore not proven for patients with a vIGA-AD 3 (see Section 2.4.2.4).

Acne (PT, AE)

A statistically significant difference to the disadvantage of upadacitinib in comparison with dupilumab was shown for the outcome of acne (PT, AE). This results in a hint of greater harm from upadacitinib in comparison with dupilumab.

2.4.2.4 Subgroups and other effect modifiers

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

- sex (female versus male)
- age (< 40 years versus ≥ 40 years)
- disease severity (vIGA-AD 3 vs. vIGA-AD 4)

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

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

Table 14: Subgroups (side effects, dichotomous) – RCT, direct comparison: upadacitinib vs. dupilumab

Study Outcome Characteristic Subgroup	Upadacitinib N	Upadacitinib Patients with event n (%)	Dupilumab N	Dupilumab Patients with event n (%)	Upadacitinib vs. dupilumab RR [95% CI][a]	Upadacitinib vs. dupilumab p-value[a]
Heads Up						
Severe AEs[b]						
Sex						
Female	165	18 (10.9)	150	2 (1.3)	8.18 [1.93; 34.67]	0.004
Male	183	13 (7.1)	194	13 (6.7)	1.06 [0.50; 2.23]	0.877
Total					Interaction:	0.004
Infections[c]						
Age						
< 40 years	228	102 (44.7)	226	96 (42.5)	1.05 [0.85; 1.30]	0.628
≥ 40 years	120	59 (49.2)	118	37 (31.4)	1.57 [1.14; 2.17]	0.006
Total					Interaction:	0.040
Eye disorders (SOC, AE)						
vIGA-AD						
3	174	17 (9.8)	171	19 (11.1)	0.88 [0.47; 1.63]	0.684
4	174	9 (5.2)	173	30 (17.3)	0.30 [0.15; 0.61]	< 0.001
Total					Interaction:	0.022

a. GLM (log-link) with treatment, subgroup variable as well as interaction term between treatment and subgroup variable as covariables.
b. Operationalized as CTCAE grade ≥ 3.
c. All AEs of the MedDRA SOC "infections and infestations" are used for the recording of infections.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; GLM: generalized linear model; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SOC: System Organ Class; vIGA-AD: validated Investigator Global Assessment for Atopic Dermatitis

Side effects

Overall rates of severe AEs (CTCAE grade ≥ 3)

There is an effect modification by the characteristic of sex for the outcome of severe AEs (CTCAE grade ≥ 3). A statistically significant difference to the disadvantage of upadacitinib in comparison with dupilumab was shown for women. For the outcome of severe AEs, this results in a hint of greater harm from upadacitinib in comparison with dupilumab. For men, there is no statistically significant difference between upadacitinib and dupilumab. This results in no hint of greater or lesser harm from upadacitinib for men; greater or lesser harm is therefore not proven.

Infections and infestations (SOC, AE)

There is an effect modification by the characteristic of age for the outcome of infections. A statistically significant difference to the disadvantage of upadacitinib in comparison with dupilumab was shown for the subgroup ≥ 40 years of age. For patients ≥ 40 years of age, this results in a hint of greater harm from upadacitinib in comparison with dupilumab for the outcome of infections and infestations (SOC, AE). For the subgroup < 40 years of age, there is no statistically significant difference between upadacitinib and dupilumab. For patients < 40 years of age, this results in no hint of greater or lesser harm from upadacitinib; greater or lesser harm is therefore not proven for patients < 40 years of age.

Eye disorders (SOC, AE)

There is an effect modification by the characteristic of disease severity for the outcome of eye disorders (SOC, AE). A statistically significant difference in favour of upadacitinib in comparison with dupilumab was shown for the subgroup of vIGA-AD 4. For patients with a vIGA-AD 4, this results in a hint of greater harm from upadacitinib in comparison with dupilumab for the outcome of eye disorders (SOC, AE). For the subgroup of vIGA-AD 3, there is no statistically significant difference between upadacitinib and dupilumab. For patients with a vIGA-AD 3, this results in no hint of greater or lesser harm from upadacitinib; greater or lesser harm is therefore not proven for patients with a vIGA-AD 3.

2.4.3 Probability and extent of added benefit

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

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.4.2 (see Table 15).

Determination of the outcome category for symptom outcomes

For the symptom outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. The classification for these outcomes is justified.

The assessment of the outcome category of the various symptom outcomes depends on the patients' baseline situation, particularly on the severity and degree of impairment caused by their symptoms. Therefore, the data at baseline are used.

Symptoms – remission (EASI 100)

The median EASI score at baseline for the patients included in the Heads Up study was above 21 (upadacitinib arm: 27.3; dupilumab arm: 25.5). The median EASI scores are thus in a serious range [18]. The outcome of remission (EASI 100) is therefore allocated to the category of serious/severe symptoms/late complications.

This concurs with the company's assessment.

Symptoms – itching (WP-NRS 0)

The median WP-NRS score was 7.5 in the upadacitinib arm and 7.7 in the dupilumab arm. According to [31], from a score of 7, itching is rated as severe. For this reason, the outcome of itching (WP-NRS) is allocated to the outcome category of serious/severe symptoms/late complications in the present benefit assessment.

This concurs with the company's assessment.

Patient-reported symptoms (HN-PGIS 0)

The median HN-PGIS score at baseline in both treatment arms was 4.0, from a maximum possible score of 6. No sufficient data are available on the allocation of the severity grade that would result in a classification as serious/severe. Therefore, this outcome is allocated to the outcome category of non-serious/non-severe symptoms/late complications.

This deviates from the assessment of the company, which allocated the outcome to the outcome category of serious/severe symptoms/late complications. From the point of view of the company, a score ≥ 4 is to be classified as serious/severe by definition, since a self-assessed score of 4 means moderately severe symptoms in the head and neck area. However, according to the HN-PGIS, moderately severe symptoms are defined as symptoms that cannot be ignored and occasionally limit daily activities. This definition of moderately severe symptoms according to the HN-PGIS is not sufficient to allow a clear classification of the outcome category as serious/severe symptoms/late complications.

Table 15: Extent of added benefit at outcome level: upadacitinib vs. dupilumab[a] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Upadacitinib vs. dupilumab** **Proportion of events (%)** **RR [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
All-cause mortality	0.3% vs. 0% 2.97 [0.12; 72.55] p = 0.505	Lesser benefit/added benefit not proven
Morbidity		
Symptoms		
Remission (EASI 100)	28.7% vs. 14.0% 2.05 [1.50; 2.79] 0.49 [0.36; 0.67][d] p < 0.001 “hint”	Outcome category: serious/severe symptoms/late complications $CI_u < 0.75$ added benefit, extent: “major”
Itching (WP-NRS 0)	26.4% vs. 8.4% 3.14 [2.12; 4.63] 0.32 [0.22; 0.47][d] p < 0.001 “hint”	Outcome category: serious/severe symptoms/late complications $CI_u < 0.75$ added benefit, extent: “major”
Patient-reported symptoms (HN-PGIS 0)	28.5% vs. 16.9% 1.69 [1.27; 2.26] 0.59 [0.44; 0.79][d] p < 0.001 “hint”	Outcome category: non-serious/non-severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: “considerable”
Health-related quality of life		
–	Outcomes from this category were not recorded	Lesser benefit/added benefit not proven
Side effects		
SAEs	3.7% vs. 2.0% 1.84 [0.74; 4.55] p = 0.189	Greater/lesser harm not proven
Severe AEs		
Female	10.9% vs. 1.3% 8.18 [1.93; 34.67] 0.12 [0.03; 0.52][d] p = 0.004 “hint”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: “major”
Male	7.1% vs. 6.7% 1.06 [0.50; 2.23] p = 0.877	Greater/lesser harm not proven
Discontinuation due to AEs	3.2% vs. 1.2% 2.72 [0.87; 8.45] p = 0.084	Greater/lesser harm not proven

Table 15: Extent of added benefit at outcome level: upadacitinib vs. dupilumab[a] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Upadacitinib vs. dupilumab** **Proportion of events (%)** **RR [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Infections		
< 40 years	44.7% vs. 42.5% 1.05 [0.85; 1.30] p = 0.628	Greater/lesser harm not proven
≥ 40 years	49.2% vs. 31.4% 1.57 [1.14; 2.17] 0.64 [0.46; 0.88][d] p = 0.006 "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: "minor"
Serious infections	1.1% vs. 0.6% 1.98 [0.36; 10.72] 0.51 [0.10; 2.78][d] p = 0.533	Greater/lesser harm not proven
Conjunctivitis (AE)	1.4% vs. 10.2% 0.14 [0.06; 0.36] p < 0.001 "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Eye disorders (AEs)		
vIGA-AD 3	9.8 vs. 11.1 0.88 [0.47; 1.63] p = 0.684	Greater/lesser harm not proven
vIGA-AD 4	5.2% vs. 17.3% 0.30 [0.15; 0.61] p < 0.001 "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Acne (AE)	18.4% vs. 3.2% 5.75 [3.09; 10.71] 0.17 [0.09; 0.32][d] p < 0.001 "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

a. Only for adults for whom 30 mg upadacitinib is the appropriate dose.
b. Probability provided if a statistically significant and relevant effect is present.
c. Depending on the outcome category, estimations of effect size use different limits based on the upper limit of the confidence interval (CI_u).
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EASI: Eczema Area and Severity Index; HN-PGIS: Head and Neck-Patient Global Impression of Severity; RR: relative risk; SAE: serious adverse event; vIGA-AD: validated Investigator Global Assessment for Atopic Dermatitis; WP-NRS: Worst Pruritus Numerical Rating Scale

2.4.3.2 Overall conclusion on added benefit

Table 16 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of upadacitinib in comparison with dupilumab

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ Remission (EASI 100): hint of an added benefit – extent: "major" ▪ Itching (WP-NRS 0) – hint of an added benefit – extent: "major"	-
Non-serious/non-severe symptoms/late complications ▪ Patient-reported symptoms (HN-PGIS): hint of an added benefit – extent: "considerable"	-
-	Serious/severe side effects ▪ Severe AEs: ▫ Women: hint of greater harm – extent: "major"
Non-serious/non-severe side effects ▪ Conjunctivitis: hint of lesser harm – extent: "considerable" ▪ Eye disorders: ▫ vIGA-AD 4: hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects ▪ Acne: hint of greater harm – extent: "considerable" ▪ Infections: ▫ ≥ 40 years: hint of greater harm – extent: "minor"
Outcomes from the category of health-related quality of life were not recorded.	
a. Effects only apply to adults for whom 30 mg upadacitinib is the appropriate dose. AE: adverse event; EASI: Eczema Area and Severity Index; HN-PGIS: Head and Neck-Patient Global Impression of Severity; vIGA-AD: validated Investigator Global Assessment for Atopic Dermatitis; WP-NRS: Worst Pruritus Numerical Rating Scale	

The overall consideration shows both positive and negative effects of upadacitinib in comparison with dupilumab, partly only for subgroups. The effect modifications by the characteristics of age and severity only occurred in non-serious/non-severe side effect outcomes and are therefore not considered further. The effect modification by the characteristic of sex, however, occurred in a serious/severe side effect outcome. For this reason, the balancing of positive and negative effects is conducted separately for men and women in the following.

Due to the limitations of the Heads Up study described in Section 2.4.1, the following overall conclusions on the added benefit only apply to adults for whom 30 mg upadacitinib is the appropriate dose. No data are available for adults for whom 15 mg upadacitinib is the appropriate dose.

Women

The positive effects, each with major extent, for the symptom outcomes of remission and itching are decisive for the conclusion on the added benefit for women. There is another positive effect with considerable extent for the outcome of patient-reported symptoms. This is accompanied by greater harm of major extent in the overall rate of severe AEs (CTCAE grade ≥ 3). The negative effect does not call into question the advantages of the symptom outcomes, but, in the overall consideration, leads to a downgrading of the extent of the added benefit. Further individual outcomes of the category of non-serious/non-severe side effects show partly greater and partly lesser harm.

In summary, there is a hint of considerable added benefit of upadacitinib in comparison with the ACT dupilumab for women with moderate to severe atopic dermatitis who are candidates for systemic therapy.

Men

The positive effects, each with major extent, for the symptom outcomes of remission and itching are decisive for the conclusion on the added benefit for men. There is another positive effect with considerable extent for the outcome of patient-reported symptoms. Individual outcomes of the category of non-serious/non-severe side effects show partly greater and partly lesser harm.

In summary, there is a hint of major added benefit of upadacitinib in comparison with the ACT dupilumab for men with moderate to severe atopic dermatitis who are candidates for systemic therapy.

The assessment described above deviates from that of the company, which derived an indication of major added benefit of upadacitinib in comparison with dupilumab in adults and adolescents 12 years and older with moderate to severe atopic dermatitis.

2.5 Subquestion 2: adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy

2.5.1.1 Approach of the company

The company did not identify any RCTs conducted in adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy, and comparing upadacitinib against the ACT dupilumab, in line with the research question defined in Section 2.2. The company therefore used the Heads Up study in adults described in Section 2.4.1 for the derivation of the added benefit for adolescents, conducting an evidence transfer.

The company did not conduct a systematic search for studies that support an evidence transfer to adolescents. It identified the 3 approval studies Measure Up 1, Measure Up 2 and AD Up

from its own study pool. The company did not conduct a search for studies with adolescents for the ACT dupilumab.

Analogous to the company's assessment, the studies Measure Up 1, Measure Up 2 and AD Up are unsuitable for the derivation of the added benefit because there was no comparison against the ACT dupilumab. Furthermore, with a treatment duration of 16 weeks (comparison against placebo), they are too short to assess long-term effects of upadacitinib on the chronic-inflammatory course of atopic dermatitis.

To check the prerequisites for an evidence transfer to adolescents, the company presented analyses on adolescents (12 to 17 years of age) of the 3 studies Measure Up 1, Measure Up 2 and AD Up as supplementary information. Below, the studies Measure Up 1, Measure Up 2 and AD Up are first described in summary form, followed by an assessment of the company's approach.

Study characteristics of Measure Up 1, Measure Up 2 and AD Up

All 3 studies are RCTs with a double-blind treatment phase of 16 weeks comparing upadacitinib in dosages of 15 mg and 30 mg daily against placebo.

They included patients 12 to 75 years of age with moderate to severe atopic dermatitis, which, according to the inclusion criteria, was analogous to the Heads Up study (see also Table 26 of the full dossier assessment). Following the double-blind treatment phase, patients entered a single-blind extension phase with either 15 mg or 30 mg upadacitinib until week 260; patients in the original placebo arms were also randomized to one of the 2 upadacitinib arms.

In the AD-Up study, patients additionally received class II TCS and/or TCI on areas with active lesions as background therapy at the beginning of the study medication and until the active lesions were under control, but no longer than up to and including treatment week 3. Between week 4 and week 24, rescue therapy was allowed in all 3 studies if there was a 50% worsening of EASI at 2 consecutive visits. In general, topical therapies were to be used first. If there was no response to these therapies after at least 7 days, systemic therapies could also be used. After week 24, rescue therapies could be used generally if EASI 50 was not achieved in comparison with baseline.

The studies Measure Up 1 and Measure Up 2 included a total of 847 and 836 patients, respectively, including 124 and 104 adolescents aged 12 to 17 years. In the Measure Up 1 study, 42 adolescents each were randomly assigned to the 15 mg upadacitinib arm and to the 30 mg upadacitinib arm, and 40 adolescents to the placebo arm. In the Measure Up 2 study, 33 adolescents were randomly assigned to the 15 mg upadacitinib arm, 35 adolescents to the 30 mg upadacitinib arm, and 36 adolescents to the placebo arm.

The AD Up study included a total of 901 patients, including 116 adolescents aged 12 to 17 years. 39 adolescents were randomly assigned to the 15 mg upadacitinib arm, 37 adolescents to the 30 mg upadacitinib arm, and 40 adolescents to the placebo arm.

Further information on the characteristics of the studies and of the interventions of the studies Measure Up 1, Measure Up 2 and AD Up can be found in Appendix D of the full dossier assessment.

Results of the Heads Up study are not transferable to adolescents

As described above, the company conducted an evidence transfer to adolescents by transferring the results of the Heads Up study in adults to adolescents. It additionally considered the analyses on adolescents from the studies Measure Up 1, Measure Up 2 and AD Up. For this purpose, it used the 15 mg upadacitinib arms and the placebo arms because 15 mg is the only approved dose for adolescents [13]. The company did not present any data for adolescents on the comparator therapy dupilumab and also had not searched for data on dupilumab. Overall, the company considered the following requirements to be fulfilled:

- There was no indication that the mechanism of action of the drug upadacitinib is different in adolescents and adults.
- The pathogenesis and clinical picture of atopic dermatitis were sufficiently similar in adolescents and adults.
- The results on efficacy and safety in the Heads Up study at week 24 and in the analyses on adolescents of the 3 approval studies at week 16 were in the same direction.
- There was an added benefit for adults.
- The ACT was identical for adolescents and adults.
- There was no important effect modification by age in the Heads Up study.

In principle, the transfer of results from adults to adolescents in the therapeutic indication of atopic dermatitis is possible in certain data constellations. Pathogenesis and clinical picture of atopic dermatitis are sufficiently similar in adolescents and adults [29,32,33]. In addition, no significant effect modification by age was observed in the Heads Up study in adults, and consistent and large effects were shown across various outcomes in the analyses on adolescents from the studies Measure Up 1, Measure Up 2 and AD Up at week 16. However, these refer exclusively to the comparison with placebo. There is no direct comparison of upadacitinib against the ACT dupilumab; the company also did not consider any other data on dupilumab in adolescents (see above).

Although various prerequisites for a transfer of evidence are met, the transfer of the results from adults in the Heads Up study to adolescents is not possible in the present data constellation. As described in Section 2.4.1, upadacitinib was administered only in the 30 mg dose in the Heads Up study, although upadacitinib is also approved in the 15 mg dose for adults. Thus, data are

only available for adults for whom a dose of 30 mg is appropriate. Due to the dose-dependent efficacy of upadacitinib, the derivation of the added benefit in the present benefit assessment is only conducted for patients for whom the 30 mg dose is the appropriate dose of upadacitinib. No data are available for adults for whom the 15 mg dose of upadacitinib is the appropriate dose. Since only the 15 mg dose is approved for adolescents, a transfer of the results from adults to adolescents is not possible in this data constellation.

2.5.2 Results on added benefit

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

2.5.3 Probability and extent of added benefit

An added benefit is not proven because the company did not present any suitable data for the assessment of the added benefit of upadacitinib in comparison with the ACT dupilumab for adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy.

The assessment described above deviates from that of the company, which derived an indication of major added benefit of upadacitinib in comparison with dupilumab in adults and adolescents 12 years and older with moderate to severe atopic dermatitis.

2.6 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of upadacitinib in comparison with the ACT is summarized in Table 17.

Table 17: Upadacitinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy[b]	Dupilumab (possibly in combination with TCS and/or TCI)	Adults for whom 30 mg is the appropriate dose: ▪ Women: hint of considerable added benefit ▪ Men: hint of major added benefit
		Adults for whom 15 mg is the appropriate dose: Added benefit not proven
		Adolescents (12-17 years)[c]: Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the approval, the therapeutic indication comprises those patients who are candidates for systemic therapy. For the determination of the ACT, adults and adolescents 12 years and older with moderate to severe atopic dermatitis are considered for whom long-term/continuous systemic therapy is indicated, as the drug upadacitinib is to be used as continuous therapy and is therefore only an option for patients for whom long-term/continuous systemic therapy is indicated.
c. Only a dose of 15 mg upadacitinib is approved for adolescents (12-17 years).

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

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

References for English extract

Please see full dossier assessment for full reference list.

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

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