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Dupilumab (atopic dermatitis in adolescents) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Dupilumab (atopische Dermatitis bei Jugendlichen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 November 2019). 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.

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Enno Schmidt, Clinic for Dermatology, University of Lübeck, Germany

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.

IQWiG employees involved in the dossier assessment:

- Jennifer Freymann
- Katharina Hirsch
- Lisa Junge
- Florina Kerekes
- Stefan Kobza
- Dorothea Sow
- Carolin Weigel
- Beate Wieseler

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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
BSA	Body Surface Area
CI	confidence interval
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IGA	Investigator's Global Assessment
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention-to-treat
LOCF	last observation carried forward
MI	multiple imputation
NRS	Numerical Rating Scale
POEM	Patient-Oriented Eczema Measure
PT	Preferred Term
RCT	randomized controlled trial
SCORAD	Scoring Atopic Dermatitis
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SOC	System Organ Class
TCI	topical calcineurin inhibitors
TCS	topical glucocorticoids
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug dupilumab. The assessment was based on a dossier compiled by the company. The dossier was sent to IQWiG on 29 August 2019.

Research question

The aim of the present report was to assess the added benefit of dupilumab in comparison with the appropriate comparator therapy (ACT) in adolescents aged 12 years and older with moderate to severe atopic dermatitis for whom systemic therapy is an option.

Table 2 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of dupilumab

Therapeutic indication	**ACT[a]**
Adolescents aged 12 years and older with moderate to severe atopic dermatitis for whom systemic treatment is an option	An individually optimized treatment regimen of topical and systemic therapy depending on the extent of the disease and taking the prior therapy into account, under consideration of the following treatments: ▪ topical class 2 to 4 glucocorticoids ▪ tacrolimus (topical) ▪ ciclosporin[b]
a: Presentation of the ACT specified by the G-BA. In addition, the G-BA provided further information on the implementation of the ACT (see text). b: Exclusively for the treatment of severe forms of a longer existing atopic dermatitis in adolescents aged 16 years and older who cannot be treated adequately with conventional therapies. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

For the implementation of the ACT, the G-BA also emphasized the assumption that other, alternative drugs would be used in case of intolerances and that neither sole placebo comparison nor unchanged continuation of inadequate (pre)treatment were considered adequate implementations of the ACT. The G-BA described that adjustment of the therapy during the relapses was assumed and was to be differentiated from therapy adjustment during the chronic phases; however, it was not to be considered an individually optimized treatment regimen within the framework of the envisaged therapeutic indication. Besides treatment of the relapses, adjustment of the treatment should also be possible during the chronic phases within the framework of the study.

The company principally followed the G-BA’s specification of the ACT, however, without stating the comments of the G-BA on the ACT.

The assessment was made by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum treatment duration of 24 weeks were used for the derivation of the added benefit.

The AD-1526 study was unsuitable for the assessment of the added benefit

For its assessment, the company used the study R668-AD-1526 (hereinafter referred to as study AD-1526) with adolescents aged 12 years and older. The study is a randomized, double-blind, controlled 3-arm study on the comparison of dupilumab (in 2 different dosages) with placebo. It included patients between 12 and < 18 years of age who had had chronic atopic dermatitis for at least one year. Study AD-1526 had a treatment duration of 16 weeks and did thus not fulfil the minimum treatment duration of 24 weeks requested in the present therapeutic indication; therefore, the company additionally used data of the study R668-AD-1224 (hereinafter referred to as CHRONOS) to update the results of study AD-1526 to 24 weeks at week 16 . However, the AD-1526 study was unsuitable to derive an added benefit of dupilumab versus the ACT.

Missing implementation of the appropriate comparator therapy

On average, the patients had severe forms of disease according to the severity classification of Eczema Area and Severity Index (EASI) and Scoring Atopic Dermatitis (SCORAD) upon study inclusion. According to the classification of the severity grades based on Investigator's Global Assessment (IGA), moderate (IGA = 3) and severe (IGA = 4) forms of disease were almost equally represented in both treatment groups. On average, about 56% of the body surface was affected by atopic dermatits. The patients included thus had moderate to severe atopic dermatitis. For this patient population, a specific drug therapy is generally indicated according to the graded scheme for the treatment of atopic dermatitis.

While in the intervention arm a specific drug therapy for the treatment of atopic dermatitis was initiated with the administration of dupilumab from day 1, drug treatment in the comparator arm was only allowed with a rescue therapy when the symptoms were intolerable. Thus, only 5 of 85 (6%) patients in the comparator arm received a rescue therapy in week 1 despite need for treatment. At week 16, the proportion of patients with rescue therapy was 59% in the comparator arm. However, at this time point only 4 of 85 (5%) patients were free (IGA = 0) or almost free (IGA = 1) of lesions and non-treatment was thus acceptable. Thus, a relevant part of the patients did not receive any drug therapy over the entire course of the study despite symptoms requiring treatment.

Transfer of the results of the age stratum ≥ 18 to < 40 years in the CHRONOS study to adolescents

The CHRONOS study including adults with moderate to severe atopic dermatitis is available in addition to the unsuitable study AD-1526 on adolescents. In the present data constellation, the results for the adults of the CHRONOS study can be transferred to the adolescent target

population, since the following characteristics of the therapeutic indication and the presented studies support the transferability:

- Pathogenesis and clinical picture of adolescents and adults are sufficiently similar in the therapeutic indication of atopic dermatitis.
- In the CHRONOS study, no significant effect modification by age is observed.
- Within the AD-1526 study, consistent and large effects across the different outcomes were shown at week 16.

In order to approach the target population of adolescents, the age stratum ≥ 18 to < 40 years from the CHRONOS study was considered for the assessment. The results at week 24 were used. Data at week 52 are not available for the relevant age stratum. The transfer was based on the outcomes that had formed the basis for the conclusion of dossier assessment A17-63 and the decision on the procedure for dupilumab in adult patients.

Results

Study pool

The age stratum ≥ 18 to < 40 years of the CHRONOS study was used for the assessment of the added benefit.

Study CHRONOS

Study characteristics

The known CHRONOS study is a randomized, double-blind, controlled, 3-arm parallel-group study on the 52-week comparison of dupilumab (with 2 different dosages) + topical glucocorticoids (TCS) with placebo + TCS in adults. The dupilumab arm, in which dupilumab doses of 300 mg were administered every 2 weeks, is relevant for the assessment.

7 days before the first administration of the study medication at the latest, all patients had to use emollients twice daily, further therapies were not allowed. With the start of the study medication, patients received a background therapy with moderate-potency TCS, which could be discontinued or reinitiated as individually required. When the symptoms persisted or worsened, treatment escalation, referred to as rescue therapy, with high-potency to very high-potency TCS, systemic therapies or phototherapy was performed. See dossier assessment A17-63 for a detailed description of the study and intervention characteristics including the restrictions of the study.

Risk of bias

See dossier assessment A17-63 for the assessment of the risk of bias of the CHRONOS study. Due to lack of data, the risk of bias of the used results of the age stratum ≥ 18 to < 40 years is rated as potentially high. Except for the outcome “itching”, the bias of the results of the total population presented as supplementary information is rated as low for all outcomes. Since the effect estimations of the total population and the subpopulation are sufficiently similar, the

certainty of results is not downgraded in the present data constellation (except for the outcome "itching") .

Transfer of the results of the age stratum ≥ 18 to < 40 years of the CHRONOS study to adolescents

Morbidity – symptoms: itching (Peak Pruritus Numerical Rating Scale [NRS])

For the symptom outcome "itching" (Peak Pruritus NRS), responder analyses for an improvement ≥ 4 points at week 24 were used. A statistically significant difference in favour of dupilumab was shown for the relevant age stratum. This resulted in a hint of an added benefit of dupilumab in comparison with the comparator therapy.

Morbidity - Patient-reported symptoms (Patient-Oriented Eczema Measure [POEM])

The mean change between week 24 and baseline was considered for patient-reported symptoms recorded using POEM. For the relevant age stratum, there was a statistically significant difference in favour of dupilumab for this outcome. The standardized mean difference (SMD) in the form of Hedges' g was considered to check the relevance of the result. The 95% confidence interval (CI) of the SMD was completely below the irrelevance threshold of –0.2. This was interpreted to be a relevant effect. This resulted in an indication of an added benefit of dupilumab in comparison with the comparator therapy.

Morbidity – Symptoms: insomnia (visual analogue scale [VAS] of the SCORAD)

For the relevant age stratum, a statistically significant difference in favour of dupilumab was shown for the mean change at week 24 versus baseline for the outcome "insomnia", measured with the SCORAD VAS on "insomnia". The SMD in the form of Hedges' g was considered to check the relevance of the result. However, the 95% CI of the SMD for the relevant age stratum was not completely outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. As a result, there was no hint of an added benefit of dupilumab versus the comparator therapy for this outcome; an added benefit is therefore not proven.

Morbidity - health status (European Quality of Life-5 Dimensions [EQ-5D] VAS)

For the age stratum ≥ 18 to < 40 years, there are no data for the outcome "health status", recorded using the EQ-5D VAS. This resulted in no hint of an added benefit of dupilumab versus the comparator therapy for this outcome; an added benefit is therefore not proven.

Health-related quality of life (Dermatology Life Quality Index [DLQI])

There is a statistically significant difference in favour of dupilumab for the proportion of patients with a DLQI score of 0 or 1 in the relevant age stratum at week 24. This resulted in an indication of an added benefit of dupilumab in comparison with the comparator therapy for this outcome.

Side effects - specific AEs

Eye disorders (System Organ Class (SOC), AE)

The company presented no data for the outcome "eye disorders (SOC)" for the age stratum ≥ 18 to < 40 years. At week 24, there was a statistically significant difference to the disadvantage of dupilumab in comparison with the comparator therapy versus baseline for the results of the total population presented as supplementary information.

The results of the outcome "any conjunctivitis or blepharitis (Preferred Term [PT])" considered as supplementary information, show a statistically significant difference to the disadvantage of dupilumab in comparison with the comparator therapy each for the relevant age stratum and the total population presented as supplementary information.

There are no data available for the outcome "eye disorders (SOC)" in the relevant age stratum ≥ 18 to < 40 years. However, there is a consistent picture of greater harm from dupilumab versus the comparator therapy for the relevant age stratum and the total population for the outcome "any conjunctivitis or blepharitis (PT)" presented as supplementary information. In the present data situation, it is assumed that there are effects for the outcome "eye disorders (SOC)" for the age stratum ≥ 18 to < 40 years which are comparable with those of the total population. Overall, this results in an indication of greater harm from dupilumab in comparison with the comparator therapy for the outcome "eye disorders (SOC)".

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

Based on the age stratum ≥ 18 to < 40 years of the CHRONOS study, there are positive effects in the outcome categories "morbidity" and "health-related quality of life" in the overall assessment for the target population of adolescents aged 12 years and older with moderate to severe atopic dermatitis, for whom systemic treatment is an option.

For the total population, there is a negative effect in the outcome category "side effects", which is caused by the outcome "eye disorders". This negative effect is confirmed by the outcome "any conjunctivitis or blepharitis" presented as supplementary information in the relevant age stratum and in the total population. As there is no meaningful effect modification by age and the outcomes "eye disorders" and "conjunctivitis or blepharitis" describe the same range of side

[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].

effects, the negative effect is also assumed to apply to the target population. However, this negative effect does not challenge the positive effects of dupilumab.

In dossier assessment A17-63, the restrictions regarding the implementation of the ACT resulted in a classification of the added benefit as non-quantifiable; this classification was maintained for the relevant age stratum in the present benefit assessment.

Depending on the data situation, the transfer of evidence between the different patient groups can lead to a downgrade of the certainty of conclusions. This aspect is not considered in the present data constellation, because the AD-1526 study shows consistently large effects.

In summary, this results in an indication of a non-quantifiable added benefit of dupilumab in comparison with the ACT for adolescents aged 12 years and older with moderate to severe atopic dermatitis for whom systemic treatment is an option.

Table 3 presents a summary of the probability and extent of the added benefit of dupilumab.

Table 3: Dupilumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit[b]**
Adolescents aged 12 years and older with moderate to severe atopic dermatitis for whom systemic treatment is an option	An individually optimized treatment regimen of topical and systemic therapy depending on the extent of the disease and taking the prior therapy into account, under consideration of the following treatments: ▪ topical class 2 to 4 glucocorticoids ▪ tacrolimus (topical) ▪ ciclosporin[c]	Indication of a non-quantifiable added benefit

a: Presentation of the ACT specified by the G-BA. For the implementation of the ACT, the G-BA also emphasized the assumption that other, alternative drugs would be used in case of intolerances and that neither sole placebo comparison nor unchanged continuation of inadequate (pre)treatment were adequate implementations of the ACT. The G-BA described that adjustment of the therapy during the relapses was assumed and was to be differentiated from therapy adjustment during the chronic phases; however, it was not to be considered an individually optimized treatment regimen within the framework of the envisaged therapeutic indication. Besides treatment of the relapses, adjustment of the treatment should also be possible during the chronic phases within the framework of the study.
b: The stratum ≥ 18 to < 40 years of the CHRONOS study was used for the assessment of the added benefit of dupilumab in comparison with the ACT in adolescents aged 12 years and older.
c: Exclusively for the treatment of severe forms of a longer existing atopic dermatitis in adolescents 16 years of age and older who cannot be treated adequately with conventional therapies.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The approach for deriving 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 was to assess the added benefit of dupilumab in comparison with the ACT in adolescents aged 12 years and older with moderate to severe atopic dermatitis for whom systemic therapy is an option.

Table 4 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of dupilumab

Therapeutic indication	**ACT**[a]
Adolescents aged 12 years and older with moderate to severe atopic dermatitis for whom systemic treatment is an option	An individually optimized treatment regimen of topical and systemic therapy depending on the extent of the disease and taking the prior therapy into account, under consideration of the following treatments: ▪ topical class 2 to 4 glucocorticoids ▪ tacrolimus (topical) ▪ ciclosporin[b]
a: Presentation of the ACT specified by the G-BA. In addition, the G-BA provided further information on the implementation of the ACT (see text). b: Exclusively for the treatment of severe forms of a longer existing atopic dermatitis in adolescents aged 16 years and older who cannot be treated adequately with conventional therapies. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

For the implementation of the ACT, the G-BA also emphasized the assumption that other, alternative drugs would be used in case of intolerances and that neither sole placebo comparison nor unchanged continuation of inadequate (pre)treatment were adequate implementations of the ACT. The G-BA described that adjustment of the therapy during the relapses was assumed and was to be differentiated from therapy adjustment during the chronic phases; however, it was not to be considered an individually optimized treatment regimen within the framework of the envisaged therapeutic indication. Besides treatment of the relapses, adjustment of the treatment should also be possible during the chronic phases within the framework of the study.

The company principally followed the G-BA's specification of the ACT, however, without stating the comments of the G-BA on the ACT (see Section 2.7.1 of the full benefit assessment).

The assessment was made by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum treatment duration of 24 weeks were used for the derivation of the added benefit. Such minimum treatment duration is also required as a rule by the G-BA. This deviates from the company's approach, which considered RCTs with a minimum treatment duration of 16 weeks for adolescent patients aged 12 years and older.

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 dupilumab (status: 28 June 2019)
- bibliographical literature search on dupilumab (last search on 4 July 2019)
- search in trial registries for studies on dupilumab (last search on 28 June 2019)

To check the completeness of the study pool:

- search in trial registries for studies on dupilumab (last search on 10 September 2019)

The check identified no additional relevant study.

2.3.1 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: dupilumab + TCS vs. placebo + TCS

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
R668-AD-1224 (CHRONOS[b,c])	No	Yes	No

a: Study sponsored by the company.
b: In the following tables, the study is referred to with this abbreviated form.
c: The age stratum ≥ 18 to < 40 years was used for the derivation of the added benefit for adolescents aged 12 years and older.
RCT: randomized controlled trial; TCS: topical glucocorticoids; vs.: versus

In the present data constellation, the age stratum ≥ 18 to < 40 years of the CHRONOS study was used for the benefit assessment of dupilumab in comparison with the ACT in adolescents aged 12 years and older. The CHRONOS study was already known from dossier assessment A17-63 [3].

This approach deviates from that of the company, which used the study R668-AD-1526 (hereinafter referred to as study AD-1526) with adolescents aged 12 years and older. Study AD-1526 had a treatment duration of 16 weeks and did thus not fulfil the minimum treatment duration of 24 weeks requested in the present therapeutic indication; therefore, the company additionally used data of the CHRONOS study to update the results of study AD-1526 at week 16 to 24 weeks. However, the AD-1526 study was unsuitable to derive an added benefit of dupilumab versus the ACT (see below).

Moreover, the company presented the single-arm extension study R668-AD-1434 [4-9] (hereinafter referred to as AD-1434) as supplementary information. This study was not used for the present benefit assessment (see Section 2.7.7 of the full dossier assessment).

The AD-1526 study was unsuitable for the assessment of the added benefit

Study AD-1526 presented by the company was unsuitable for assessing the added benefit of dupilumab versus the ACT. This is justified below.

Study characteristics

Study design

The study AD-1526 [10-17] is a randomized, double-blind, controlled 3-arm study on the comparison of dupilumab (in 2 different dosages) with placebo. Treatment duration was 16 weeks. The planned follow-up observation period for the individual outcomes was 12 weeks. Alternatively, patients under 18 years of age had the opportunity to participate in the open, single-arm extension study AD-1434. Patients who exceeded the age of 18 years during the course of AD-1526 were allowed to switch to the R668-AD-1225 study with adults.

It included patients between 12 and < 18 years of age who had had chronic atopic dermatitis for at least one year. Moreover, the patients had to have responded inadequately to topical treatments within 6 months before study inclusion. Alternatively, the study could include adolescents for whom topical treatment was not medically advisable (e.g. due to a lack of tolerability or because of safety risks). Inadequate response was defined as not achieving and not maintaining remission or lower disease activity (IGA 0-2) despite daily treatment with moderate-potency to high-potency TCS with or without calcineurin inhibitors (TCI) for at least 28 days or the maximally permitted treatment duration according to the approval. Documented systemic treatment in the last 6 months prior to study inclusion was also considered an insufficient response to topical therapies.

The severity of the disease was defined using the following criteria: proportion of the affected body surface (Body Surface Area [BSA]) ≥ 10, EASI ≥ 16 and IGA ≥ 3. For the present benefit assessment, this definition of the severity grade was rated as adequate representation of moderate to severe atopic dermatitis (see Section 2.7.2 of the full dossier assessment).

A total of 251 patients of the study were randomly assigned (1:1:1) to subcutaneous treatment with dupilumab once every 2 weeks (N = 82), dupilumab once every 4 weeks[4] (N = 84) or placebo once every 2 weeks (N = 85). The dosage was weight-dependent, patients < 60 kg received 200 mg, patients ≥ 60 kg received 300 mg. On day 1, an initial subcutaneous dose of 400 mg (< 60 kg) or 600 mg (≥ 60 kg) was administered in the dupilumab arms in compliance with the approval [18,19].

[4] A dosage of 200 or 300 mg every 4 weeks is not approved in Germany and was therefore not considered further.

Background therapy and rescue therapy

7 days before the first administration of the study medication at the latest, all patients had to use emollients as background therapy at least twice daily, further therapies were not allowed. In the case of intolerable symptoms, a drug therapy was initiated at the investigator's discretion from day 1, which was referred to in the study as rescue therapy. If possible, topical treatment with moderate-potency to high-potency TCS and/or topical calcineurin inhibitors (TCI) should be initiated and only be escalated to systemic treatment in patients who had achieved no adequate improvement after topical therapy for at least 7 days. Application of TCI was restricted to problematic areas (e.g. face, neck, genital area). Application of systemic glucocorticoids and systemic non-steroidal immunosuppressants such as ciclosporin resulted in treatment discontinuation. Patients who discontinued treatment were requested to further participate in all planned study visits.

Missing implementation of the ACT

On average, when included in the study the patients had severe forms of disease according to the severity classification of EASI [20] and SCORAD [21]. According to the classification of the severity grades based on IGA [22], moderate (IGA = 3) and severe (IGA = 4) forms of disease were almost equally represented in both treatment groups. On average, about 56% of the body surface were affected by atopic dermatits. For the patient population with moderate to severe atopic dermatitis, a specific drug therapy is generally indicated according to the graded scheme for the treatment of atopic dermatitis [21,23].

While in the intervention arm a specific drug therapy for the treatment of atopic dermatitis was initiated with the administration of dupilumab from day 1, drug treatment in the comparator arm was only allowed with a rescue therapy when the symptoms were intolerable. Thus, only 5 of 85 (6%) patients in the comparator arm received a rescue therapy in week 1 despite need for treatment. At week 16, the proportion of patients with rescue therapy was 59% in the comparator arm. However, at this time point only 4 of 85 (5%) patients were free (IGA = 0) or almost free (IGA = 1) of lesions and non-treatment was thus acceptable. Thus, a relevant part of the patients did not receive any drug therapy over the entire course of the study despite symptoms requiring treatment.

The ACT (an individually optimized treatment regimen) comprised both a reactive and a proactive treatment approach in the therapeutic indication of atopic dermatitis. Within the reactive treatment approach, topical therapies are discontinued after the acute lesions have subsided, they are only resumed after the recurrence of lesions. Within the proactive treatment approach, the affected skin areas were treated with topical therapies also after the skin changes had subsided (intermittent subsequent treatment; once to twice weekly) [21,23,24]. A rescue therapy can basically be part of an individually optimized treatment regimen in the sense of a reactive treatment approach. However, with the rescue therapy that was only applied in case of intolerable symptoms, neither the reactive nor the proactive treatment approach was implemented in the comparator arm of study AD-1526. The study documents provide no

information on the extent to which the proactive treatment approach would have presented the individually optimized treatment strategy for some of the patients. Altogether, the ACT of an individually optimized treatment regimen was not implemented in study AD-1526.

Inadequate imputation of the data

Since the duration of treatment in study AD-1526 did not correspond to the minimum treatment duration of 24 weeks in the present therapeutic indication, the company used the results of the CHRONOS study with adult patients to impute the results of the AD-1526 study to 24 weeks. The company only imputed the results of study AD-1526 to week 24 if there were significant effects at week 16. Moreover, results on side effect outcomes were also imputed when there were significant results in adults in the CHRONOS study at week 24. In both cases, imputation was only performed in case of homogeneous data situations.

In contrast to study AD-1526, patients in the comparator arm of the CHRONOS study received – with certain restrictions – an individually optimized treatment regimen (see below). Therewith, the studies AD-1526 and CHRONOS compare dupilumab with different therapies (AD-1526: dupilumab versus placebo, CHRONOS: dupilumab + TCS vs. placebo + TCS). This can also be seen from the fact that at week 16 a higher proportion of patients were free of lesions or almost free of lesions (IGA 0 or 1) in the CHRONOS study (with about 16% of the patients in the placebo arm and about 39% in the intervention arm) than in the AD-1526 study (placebo arm: about 5% of the patients, intervention arm: about 24% of the patients). The imputation of the data of study AD-1526 from week 16 to week 24 performed by the company using the data of the CHRONOS study was therefore not appropriate.

Moreover, it is unclear why the company imputed the data to week 24, although the CHRONOS study includes data on week 52 and thus on a significantly longer course of treatment.

Study CHRONOS

The CHRONOS study has already been used in dossier assessment A17-63 [3] for the assessment of the added benefit of dupilumab versus the ACT in adults with moderate to severe atopic dermatitis for whom systemic therapy is an option. The study is a randomized, double-blind, controlled, 3-arm parallel-group study on the comparison of dupilumab (with 2 different dosages) + TCS with placebo + TCS over 52 weeks. A total of 740 patients were assigned to treatment with dupilumab 300 mg once weekly[5] (N = 319), dupilumab 300 mg once every 2 weeks (N = 106) or placebo once weekly, subcutaneously (N = 315).

7 days before the first administration of the study medication at the latest, all patients had to use emollients twice daily, further therapies were not allowed. With the start of the study medication, patients received a background therapy with moderate-potency TCS, which could be discontinued or reinitiated as individually required. When the symptoms persisted or

[5] A dosage of 300 mg once weekly is not approved in Germany and was therefore not considered further in the present benefit assessment.

worsened, treatment escalation, referred to as rescue therapy, with high-potency to very high-potency TCS, systemic therapies or phototherapy was performed.

See dossier assessment A17-63 [3] for a detailed description of the study and intervention characteristics of the already known CHRONOS study.

Transfer of the results of the age stratum ≥ 18 to < 40 years to adolescents

Under certain circumstances, results can be transferred from one population to another one for which no or only insufficient data are available. In the present situation, results of RTC AD-1526 are available for adolescents with moderate to severe atopic dermatitis, for whom systemic treatment is an option. However, this study is unsuitable for answering the research question of the present benefit assessment, since, as a central point, the ACT was not implemented (see above). Moreover, treatment duration was too short to permit conclusions on the added benefit of long-term dupilumab administration in atopic dermatitis.

In the present data constellation, the results for the adults of the CHRONOS study can be transferred to the adolescent target population, since the following characteristics of the therapeutic indication and the presented studies support the transferability:

- Pathogenesis and clinical picture of adolescents and adults are sufficiently similar in the therapeutic indication of atopic dermatitis. [23,25,26].
- In the CHRONOS study, no significant effect modification by age is observed.
- Within the AD-1526 study, consistent and large effects across the different outcomes were shown at week 16.

In order to approach the target population of adolescents, the age stratum ≥ 18 to < 40 years from the CHRONOS study was considered for the assessment. This stratum comprised 52 patients in the relevant intervention arm and 189 patients in the comparator arm. The results at week 24 were used. Data at week 52 are not available for the relevant age stratum. The transfer was based on the outcomes that had formed the basis for the conclusion of dossier assessment A17-63 [3] and the decision on the procedure for dupilumab in adult patients [27,28]. The patient characteristics of the age stratum ≥ 18 to < 40 years are presented in Table 13 in Appendix A of the full dossier assessment; they are particularly comparable to those of the total population with regard to the disease severity at baseline. Data on prior therapies are not available for the relevant age stratum. For information on patient characteristics and prior therapies of the total population see dossier assessment A17-63 [3].

The results of study AD-1526 on the outcomes of dossier assessment A17-63 used in the present benefit assessment are presented as supplementary information in Appendix B of the full dossier assessment.

Limitations of the CHRONOS study

In the CHRONOS study, the option of a proactive therapeutic approach was not available to the patients. While, with the continuous administration of dupilumab, the patients in the dupilumab arm underwent a therapeutic strategy comparable to the proactive therapeutic approach, patients in the comparator arm received exclusively reactive treatment.

Moreover, all patients of the comparator arm received predetermined uniform treatment with moderate-potency TCS and/or TCI without consideration of the prior therapy at the start of the study, despite previous inadequate response to topical (and /or systemic) therapies. An individual therapeutic strategy was thus not planned upon entry in the study.

Within the first 2 treatment weeks, the use of a rescue therapy resulted in a discontinuation of the study medication. It remains unclear whether the background therapy was continued for these patients, in which case no comparison of dupilumab with the comparator therapy but rather of background therapies would have been made.

These limitations were considered in the derivation of the added benefit of dupilumab versus the comparator therapy.

A detailed representation of the limitations of the CHRONOS study is found in dossier assessment A17-63 [3].

Summary

The age stratum ≥ 18 to < 40 years of the CHRONOS study was used for the assessment of the added benefit of dupilumab in comparison with the ACT in adolescents aged 12 years and older with moderate to severe atopic dermatitis for whom systemic therapy is an option. The AD-1526 study was unsuitable for the derivation of an added benefit in comparison with the ACT. The results of the study AD-1526 are presented as supplementary information in Appendix B of the full dossier assessment.

Section 2.6 contains a reference list for the CHRONOS study included.

2.4 Results on added benefit

2.4.1 Outcomes included

In the present data constellation, only those outcomes were used that had formed the basis for the conclusion of dossier assessment A17-63 and the decision on the procedure for dupilumab in adult patients. These are the following patient-relevant outcomes:

- Morbidity
  - Itching, measured via a Peak Pruritus NRS
  - Patient-reported symptoms, recorded with POEM
  - Insomnia recorded with the VAS of the SCORAD

- Health status, measured with the (EQ-5D) VAS
- Health-related quality of life, measured with the DLQI
- Side effects
  - Eye disorders (SOC))
  - Presented as supplementary information: conjunctivitis or blepharitis (PT)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes (see Section 2.7.4 of the full dossier assessment).

2.4.2 Risk of bias

For information on the assessment of the risk of bias across outcomes of the CHRONOS study, see dossier assessment A17-63 [3].

Since the relevant age stratum (≥ 18 to < 40 years) only comprised 60% of the total population of the CHRONOS study and information on treatment and study discontinuations as well as response rates of the questionnaires for the age stratum were lacking, adherence to the intention-to-treat (ITT) principle cannot be assessed for this stratum. Therefore, the risk of bias of the results of the subpopulation is rated as potentially high. Except for the outcome "itching", the bias of the results of the total population presented as supplementary information was rated as low for all outcomes. This was due to the sufficiently high response rates as well as adequate imputation strategies (last observation carried forward [LOCF] for dichotomous as well as multiple imputation [MI] for continuous outcome operationalizations). Since the effect estimations of the total population and of the relevant age stratum are sufficiently similar, the certainty of results of the effects is not downgraded in the relevant age stratum on the basis of the present data constellation.

The bias of the results on the outcome "itching" in the total population is considered to be potentially high, because the proportion of the values to be imputed was more than 20% until week 24 or the group difference was above 5 percentage points. Accordingly, a high risk of bias was also assumed in the relevant age stratum and the certainty of results was downgraded.

2.4.3 Results

Table 6 and Table 7 summarize the results on the comparison of dupilumab + TCS with placebo + TCS at week 24 in adult patients aged ≥ 18 to < 40 years with moderate to severe atopic dermatitis for whom systemic treatment is an option. The results of the total population are presented as supplementary information. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The results on the outcomes EASI 75, EASI 90, SCORAD 75 and SCORAD 90 are presented as supplementary information each for the age stratum ≥ 18 to < 40 years and for the total population of the CHRONOS study.

Table 6: Results (morbidity; health-related quality of life, side effects, dichotomous) – RCT, direct comparison: dupilumab + TCS vs. placebo + TCS

Study **Outcome category** **Outcome**	**Dupilumab + TCS**		**Placebo + TCS**		**Dupilumab + TCS vs. placebo + TCS**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
CHRONOS (week 24)					
Morbidity					
symptoms					
itching – Peak Pruritus NRS improvement by ≥ 4 points					
stratum ≥ 18 to < 40 years	50	31 (62.0)	182	57 (31.3)	1.94 [1.43; 2.62]; < 0.001
total population (supplementary information)	*102*	*66 (64.7)*	*299*	*100 (33.4)*	*1.91 [1.54; 2.36]; < 0.001*
Health-related quality of life					
DLQI (0 or 1)					
stratum ≥ 18 to < 40 years	52	17 (32.7)	189	29 (15.3)	2.13 [1.27; 3.55]; 0.004
total population (supplementary information)	*106*	*35 (33.0)*	*315*	*47 (14.9)*	*2.24 [1.54; 3.27]; < 0.001*
Side effects[b]					
eye disorders (SOC, AEs)					
stratum ≥ 18 to < 40 years				ND	
total population (supplementary information)	*110*	*26 (23.6)*	*315*	*26 (8.3)*	*2.86 [1.74; 4.72][c]; < 0.001[d]*
supplementary information: any conjunctivitis or blepharitis[e] (PT, AEs)					
stratum ≥ 18 to < 40 years	55	7 (12.7)	189	8 (4.2)	3.01 [1.14; 7.94][c]; 0.023[d]
total population (supplementary information)	*110*	*14 (12.7)*	*315*	*17 (5.4)*	*2.36 [1.20; 4.63][c]; 0.011[d]*

a: unless stated otherwise; RR, CI and p-value from logistic regression adjusted according to severity of the atopic dermatitis (IGA) at baseline and region
b: Presentation of the results of the Safety Analysis Set. For this analysis, patients who received an intervention regimen other than the one assigned were allocated to the intervention group with the lowest dosage. Data of the Full Analysis Set are not available.
c: RR normal approximation; CI asymptotic
d: Institute's calculation, unconditional exact test (CSZ method according to [29]).
e: PTs on conjunctivitis or blepharitis which occurred in the course of the study

AE: adverse event; CI: confidence interval; DLQI: Dermatology Life Quality Index; IGA: Investigator Global Assessment; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; NRS: Numerical Rating Scale; PT: preferred term; RCT: randomized controlled trial; RR: relative risk; SOC: System Organ Class; TCS: topical glucocorticoids; vs.: versus

Table 7: Results (morbidity, continuous) – RCT, direct comparison: dupilumab + TCS vs. placebo + TCS

Study Outcome category	Dupilumab + TCS			Placebo + TCS			Dupilumab + TCS vs. placebo + TCS
Outcome	**N[a]**	**Values at baseline mean (SD)**	**Change at week 24 mean (SE)[b]**	**N[a]**	**Values at baseline mean (SD)**	**Change at week 24 mean (SE)[b]**	**MD [95% CI]; p-value[b]**
CHRONOS (week 24)							
Morbidity							
symptoms							
patient-reported symptoms (POEM)[c,d]							
stratum ≥ 18 to < 40 years	52	20.5 (5.2)	−12.9 (0.92)	189	20.4 (6.0)	−7.2 (0.49)	−5.71 [−7.72; −3.71]; < 0.001 Hedges' g[e]: −0.87 [−1.19; −0.56]
total population (supplementary information)	*106*	*20.3 (5.7)*	*−13.5 (0.64)*	*315*	*20.0 (6.0)*	*−6.8 (0.38)*	*−6.62 [−8.05; −5.19]; < 0.001* *Hedges' g[e]: −1.02 [−1.25; −0.79]*
insomnia – SCORAD VAS[c, d]							
stratum ≥ 18 to < 40 years	52	5.4 (3.3)	-3.7 (0.28)	189	4.9 (3.22)	−2.87 (0.15)	−0.83 [−1.43; −0.23]; 0.007 Hedges' g[e]: −0.42 [−0.73; −0.11]
total population (supplementary information)	*106*	*5.6 (3.2)*	*−3.8 (0.20)*	*315*	*4.9 (3.3)*	*−2.8 (0.12)*	*−1.00 [−1.45; −0.55]; < 0.001* *Hedges' g[e]: −0.49 [−0.71; −0.27]*
health status							
EQ-5D VAS[c,f]							
stratum ≥ 18 to < 40 years					ND		
total population (supplementary information)	*106*	*57.8 (22.5)*	*20.0 (1.67)*	*315*	*56.5 (23.7)*	*13.3 (0.99)*	*6.7 [2.93; 10.45]; < 0.001* *Hedges' g[e]: 0.39 [0.17; 0.61]*

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at baseline (possibly at other time points) may be based on other patient numbers.
b: Calculated using an ANCOVA model; treatment, baseline value, region and severity of the atopic dermatitis (IGA) as factors.
c: Imputation of missing values using MI.
d: A high value indicates severe symptoms; a negative group difference corresponds to an advantage of dupilumab.
e: Institute's calculation of mean difference and CI.
f: Higher values reflect a better health status; a positive group difference corresponds to an advantage of dupilumab.

ANCOVA: analysis of covariance; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; IGA: Investigator's Global Assessment; MD: mean difference; MI: multiple imputation; N: number of analysed patients; ND: no data; POEM: Patient-Oriented Eczema Measure; RCT: randomized controlled trial; SCORAD: SCORing Atopic Dermatitis; SD: standard deviation; SE: standard error; TCS: topical glucocorticoids; VAS: visual analogue scale; vs.: versus

As described in Section 2.3.1, the results of the age stratum ≥ 18 to < 40 years of the CHRONOS study were used to derive conclusions on the added benefit of dupilumab in adolescents aged 12 years and older.

Based on the available data, at most hints, e.g. of an added benefit, can be determined for the outcome "itching" due to the high risk of bias, and at most indications can be determined for all other outcomes.

Morbidity

Symptoms (itching – Peak Pruritus NRS)

For the symptom outcome "itching" (Peak Pruritus NRS), responder analyses were used for an improvement ≥ 4 points at week 24. A statistically significant difference in favour of dupilumab was shown for the relevant age stratum. This effect was also shown for the total population presented as supplementary information. The high proportion of imputed values of more than 20% in the total population provides a hint of an added benefit of dupilumab versus the comparator therapy. Data on the proportion of imputed values at week 24 are not available for the relevant age stratum.

Analogous to the assessment in A17-63 [3], the outcome "itching" (Peak Pruritus NRS) is assigned to the outcome category non-serious/ non-severe symptoms/late complications.

Patient-reported symptoms (POEM)

The mean change between week 24 and baseline was considered for patient-reported symptoms recorded using POEM. There was a statistically significant difference in favour of dupilumab for this outcome for the relevant age stratum and for the total population presented as supplementary information. The SMD in the form of Hedges' g was considered to check the relevance of the respective result. For the relevant age stratum and the total population, the 95% CI of the SMD was completely below the irrelevance threshold of –0.2. This was interpreted to be a relevant effect. This resulted in an indication of an added benefit of dupilumab in comparison with the comparator therapy.

Analogous to the assessment in A17-63 [3], the outcome "patient-reported symptoms (POEM)" is assigned to the outcome category non-serious/ non-severe symptoms/late complications.

Symptoms: insomnia (SCORAD-VAS)

For the mean change at week 24 versus baseline, a statistically significant difference in favour of dupilumab was shown for the relevant age stratum and for the total population presented as supplementary information for the outcome "insomnia", measured with the SCORAD VAS on "insomnia". The SMD in the form of Hedges' g was considered to check the relevance of the result. However, the 95% CI of the SMD for the relevant age stratum was not completely outside the irrelevance range of −0.2 to 0.2. In contrast to this, the 95% CI of the SMD of the total population was completely below the irrelevance threshold of –0.2. this was interpreted to be a relevant effect.

Overall, a relevance of this effect for the age stratum ≥ 18 to < 40 years cannot be derived. As a result, there was no hint of an added benefit of dupilumab versus the comparator therapy for this outcome; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

For the age stratum ≥ 18 to < 40 years, there are no data for the outcome "health status", recorded using the EQ-5D VAS. For the results presented as supplementary information, there is a statistically significant difference in favour of dupilumab at week 24 versus baseline. The SMD in the form of Hedges' g was considered to check the relevance of the result. However, the 95% CI of the SMD was not completely outside the irrelevance range of −0.2 to 0.2. A relevance of the effect can therefore not be derived.

Overall, there was no hint of an added benefit of dupilumab versus the comparator therapy for this outcome; an added benefit is therefore not proven.

Health-related quality of life

DLQI

There is a statistically significant difference in favour of dupilumab for the proportion of patients with a DLQI score of 0 or 1 in the relevant age stratum at week 24. This effect was also shown for the total population presented as supplementary information. This resulted in an indication of an added benefit of dupilumab in comparison with the comparator therapy for this outcome.

Side effects

Specific AEs

Eye disorders (SOC, AE)

The company presented no data for the outcome "eye disorders" for the age stratum ≥ 18 to < 40 years. At week 24 versus baseline, there was a statistically significant difference to the disadvantage of dupilumab in comparison with the comparator therapy for the results of the total population presented as supplementary information.

In addition, the present benefit assessment additionally considered the outcome "any conjunctivitis or blepharitis (PT)". This outcome comprises any PTs on conjunctivitis or blepharitis which occurred in the course of the study. Recording of this outcome was prespecified in the AD-1526 study. Recording of this outcome was prespecified in the AD-1526 study. For the CHRONOS study, a joint analysis of the events of the PTs on conjunctivitis and blepharitis was performed post hoc. There was a statistically significant difference to the disadvantage of dupilumab versus the comparator therapy. The results of the total population presented as supplementary information are comparable with those of the age stratum ≥ 18 to < 40 years.

There are no data available for the outcome “eye disorders (SOC)” in the relevant age stratum ≥ 18 to < 40 years. However, there is a consistent picture of greater harm from dupilumab versus the comparator therapy for the relevant age stratum and the total population for the outcome “any conjunctivitis or blepharitis (PT)” presented as supplementary information. In the present data situation, it is assumed that there are effects for the outcome “eye disorders (SOC)” for the age stratum ≥ 18 to < 40 years which are comparable with those of the total population. Overall, this results in an indication of greater harm from dupilumab in comparison with the comparator therapy for the outcome “eye disorders (SOC)”.

2.4.4 Subgroups and other effect modifiers

Explanations on the assessment of subgroups and other effect modifiers for the CHRONOS study at week 52 can be found in dossier assessment A17-63 [3].

A possible effect modification by age at week 24 was also considered in the present benefit assessment. An interaction was found for the outcome EASI-75 presented as supplementary information in Appendix C of the full dossier assessment (p = 0.0406). This interaction has an impact on the importance of the results for the overall population, as it implies an increase of the effect towards older age.

At week 24, there is no important effect modification by age across the considered outcomes for the CHRONOS study despite this interaction. The transfer of the results from the age group ≥ 18 to < 40 years to the target population of young people aged ≥ 12 to < 18 years was thus not called into question.

2.5 Probability and extent of added benefit

The various outcome categories and the effect sizes were considered for the derivation of probability and extent of the added benefit at outcome level. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

Table 8 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 8: Positive and negative effects from the assessment of dupilumab + TCS compared with placebo + TCS[a]

Positive effects	**Negative effects**
Outcome category: non-serious/non-severe symptoms/late complications: ▪ itching (Peak Pruritus NRS): hint of an added benefit – extent: "considerable" ▪ patient-reported symptoms (POEM): indication of an added benefit – extent: "non-quantifiable"	Outcome category: non-serious/non-severe side effects: ▪ eye disorders: indication of greater harm – extent "considerable"[b]
Outcome category: "health-related quality of life": ▪ DLQI (0 or 1): indication of an added benefit – extent: "considerable"	-
a: The stratum ≥ 18 to < 40 years of the CHRONOS study is used for the assessment of the added benefit of dupilumab in comparison with the ACT in adolescents aged 12 years and older. b: The derivation is based on the results of the total population, because there are no results on the relevant age stratum for this outcome. However, there are consistent effects in the outcome "any conjunctivitis or blepharitis" presented as supplementary information for the relevant age group and the total population; in the present data situation, it is therefore assumed that for the outcome eye disorders (SOC) there are effects for the age group ≥ 18 to < 40 years that are comparable to those of the total population. ACT: appropriate comparator therapy; DLQI: Dermatology Life Quality Index; NRS: Numerical Rating Scale; POEM: Patient-Oriented Eczema Measure; SOC: System Organ Class; TCS: topical glucocorticoids	

Based on the age stratum ≥ 18 to < 40 years of the CHRONOS study, there are positive effects in the outcome categories "morbidity" and "health-related quality of life" in the overall assessment for the target population of adolescents aged 12 years and older with moderate to severe atopic dermatitis, for whom systemic treatment is an option.

For the total population, there is a negative effect in the outcome category "side effects", which is caused by the outcome "eye disorders" (data on this outcome for the relevant age stratum of patients ≥ 18 to < 40 years are missing). This negative effect is confirmed by the outcome "any conjunctivitis or blepharitis" presented as supplementary information in the relevant age stratum and in the total population. As there is no significant effect modification by age and the outcomes "eye disorders" and "any conjunctivitis or blepharitis" describe the same range of side effects, it can be assumed that the negative effect also affects the target population. This negative effect does not challenge the positive effects of dupilumab.

In dossier assessment A17-63, the restrictions regarding the implementation of the ACT (see Section 2.3.1) resulted in a classification of a non-quantifiable added benefit; the classification of a non-quantifiable added benefit is maintained for the relevant age stratum in the present benefit assessment.

Depending on the data situation, the transfer of evidence between the different patient groups can lead to a downgrade of the certainty of conclusions. This aspect is not considered in the present data constellation, because the AD-1526 study shows consistently large effects.

In summary, this results in an indication of a non-quantifiable added benefit of dupilumab in comparison with the ACT for adolescents with moderate to severe atopic dermatitis for whom systemic treatment is an option.

Table 9 summarizes the result of the assessment of the added benefit of dupilumab in comparison with the ACT.

Table 9: Dupilumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit[b]**
Adolescents aged 12 years and older with moderate to severe atopic dermatitis for whom systemic treatment is an option	An individually optimized treatment regimen of topical and systemic therapy depending on the extent of the disease and taking the prior therapy into account, under consideration of the following treatments: ▪ topical class 2 to 4 glucocorticoids ▪ tacrolimus (topical) ▪ ciclosporin[c]	Indication of a non-quantifiable added benefit

a: Presentation of the ACT specified by the G-BA. For the implementation of the ACT, the G-BA also emphasized the assumption that other, alternative drugs would be used in case of intolerances and that neither sole placebo comparison nor unchanged continuation of inadequate (pre)treatment were considered adequate implementations of the ACT. The G-BA described that adjustment of the therapy during the relapses was assumed and was to be differentiated from therapy adjustment during the chronic phases; however, it was not to be considered an individually optimized treatment regimen within the framework of the envisaged therapeutic indication. Besides treatment of the relapses, adjustment of the treatment should also be possible during the chronic phases within the framework of the study.
b: The stratum ≥ 18 to < 40 years of the CHRONOS study was used for the assessment of the added benefit of dupilumab in comparison with the ACT in adolescents aged 12 years and older.
c: Exclusively for the treatment of severe forms of a longer existing atopic dermatitis in adolescents 16 years of age and older who cannot be treated adequately with conventional therapies.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit based on the results of the study AD-1526.

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

2.6 List of included studies

Blauvelt A, De Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet 2017; 389(10086): 2287-2303.

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Please see full dossier assessment for full reference list.

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4. Regeneron Pharmaceuticals. An open-label extension study to assess the long-term safety and efficacy of dupilumab in patients ≥6 month to <18 years of age with atopic dermatitis: study R668-AD-1434; Zusatzanalysen [unpublished]. 2019.

5. Regeneron Pharmaceuticals. An open-label extension study to assess the long-term safety and efficacy of dupilumab in patients ≥6 month to <18 years of age with atopic dermatitis: study R668-AD-1434; clinical study protocol amendment 3 [unpublished]. 2017.

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