IQWiG Reports – Commission No. A20-123

Dupilumab (atopic dermatitis, children 6 to 11 years of age) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Dupilumab (atopische Dermatitis, 6 bis 11 Jahre) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 March 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
Dupilumab (atopic dermatitis, children 6 to 11 years of age) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
17 December 2021

Internal Commission No.
A20-123

Address of publisher
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 Medical Centre Schleswig-Holstein – Campus 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

- Marina Woeste
- Ulrich Grouven
- Charlotte Hecker
- Lisa Junge
- Katrin Nink
- Annette Pusch-Klein
- Dorothea Sow
- Carolin Weigel

Keywords: Dupilumab, Dermatitis – Atopic, Child, Benefit Assessment, NCT02260986, NCT03345914

Table of contents

List of tables[2]

Page

[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
BfArM	Federal Institute for Drugs and Medical Devices
BMG	Federal Ministry of Health
CI	confidence interval
CMQ	Customized MedDRA Query
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)
LOCF	last observation carried forward
MedDRA	Customized Medical Dictionary for Regulatory Activities
MI	multiple imputation
NRS	Numerical Rating Scale
PEI	Paul Ehrlich Institute
POEM	Patient-Oriented Eczema Measure
RCT	randomized controlled trial
SCORAD	SCORing Atopic Dermatitis
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SOC	System Organ Class
SPC	Summary of Product Characteristics
TCI	topical calcineurin inhibitor
TCS	topical corticosteroids
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug dupilumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 17 December 2020.

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 children 6 to 11 years of age with severe atopic dermatitis who are candidates for systemic therapy.

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]
Children 6 to 11 years of age with severe atopic dermatitis who are candidates for systemic therapy	An individually optimized treatment regimen depending on the extent of the disease and taking the prior therapy into account, under consideration of the following treatments: ▪ topical class 2 to 3 glucocorticoids ▪ tacrolimus (topical)
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). 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 flares was assumed and was to be differentiated from therapy adjustment during the chronic phases; however, the option of adjustment during the flares alone was not to be considered an individually optimized treatment regimen within the framework of the envisaged therapeutic indication. In addition to the treatment of relapses, it should also be possible to adjust the therapy in the chronic phases of the study. Systemic glucocorticoids may be indicated in children as part of short-term relapse treatment.

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

Study AD-1652 unsuitable for the assessment of the added benefit

In addition to the R668-AD-1224 study (hereinafter referred to as CHRONOS; see below), the company used the R668-AD-1652 study (hereafter referred to as the AD-1652 study) for its assessment. AD-1652 is a randomized, double-blind, controlled study on the comparison of dupilumab (in different dosages and dosing intervals) with placebo. The treatment duration was 16 weeks. The study included patients between 6 and < 12 years of age who had had chronic atopic dermatitis for at least one year. All of the 367 patients of the study were randomly assigned (1:1:1) to subcutaneous treatment with dupilumab once every 2 weeks, dupilumab once every 4 weeks or placebo once every 2 or 4 weeks. The patients also received a standardized background therapy with moderate-potency topical corticosteroids (TCS) in addition to emollients. Treatment escalations were possible within the framework of a rescue therapy. Overall, there were limitations regarding the implementation of the ACT.

In order to present the results for the target population over 24 weeks, which is required for chronic diseases, the company also used results from the CHRONOS study with adults with moderate to severe atopic dermatitis at week 52 in order to transfer these results to the target population of children aged 6 to 11 years with severe atopic dermatitis.

With a treatment duration of 16 weeks, the AD-1652 study is too short to assess long-term effects of dupilumab on the chronic-inflammatory course of atopic dermatitis. However, the AD-1652 study can be used to investigate the transferability of the results of the CHRONOS study to children 6 to 11 years of age.

Transfer of the results of the age stratum ≥ 18 to < 40 years to children aged 6 to 11 years

The 52-week CHRONOS study including adults with moderate to severe atopic dermatitis is available in addition to the AD-1652 study on children from 6 to 11 years of age. In the present data constellation, the results for the adults of the CHRONOS study can be transferred to the paediatric target population, since the following characteristics of the therapeutic indication and the presented studies support the transferability:

- Pathogenesis and clinical picture of children from 6 to 11 years and adults are sufficiently similar in the therapeutic indication of atopic dermatitis.
- In the CHRONOS study, no significant effect modification by age and severity of the disease was observed.
- Overall, the AD-1652 study showed consistent and large effects across the different outcomes at week 16, both within the CHRONOS study and compared to it at week 24 and week 52.

In order to approach the target population, the age stratum ≥ 18 to < 40 years with moderate to severe atopic dermatitis from the CHRONOS study was considered for the assessment. The results at week 52 were used. 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) + 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 background therapy with moderate-potency TCS, which could be discontinued or reinitiated as required for each individual patient. 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

For information on the assessment of the risk of bias across outcomes of the CHRONOS study, see dossier assessment A17-63. Analogous to the procedure in A20-01, the risk of bias was rated as high for all results of the outcomes included in the present benefit assessment for patients in the age stratum ≥ 18 to < 40 years.

Results of the age stratum ≥ 18 to < 40 years of the CHRONOS study

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 52 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 versus the comparator therapy.

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

For patient-reported symptoms recorded using POEM, the mean change at week 52 compared to baseline was considered. For the relevant age stratum, there was a statistically significant and relevant difference in favour of dupilumab for this outcome. This resulted in a hint of an added benefit of dupilumab versus the comparator therapy.

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

For the relevant age stratum, a statistically significant and relevant difference in favour of dupilumab was shown for the mean change at week 52 versus baseline for the outcome "insomnia", measured with the SCORAD VAS on insomnia. This resulted in a hint of an added benefit of dupilumab versus the comparator therapy.

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

For the outcome "health status", recorded using the EQ-5D VAS, no statistically significant difference between the treatment groups was shown for the relevant age stratum for the mean change at week 52 compared to baseline. 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-related quality of life (Dermatology Life Quality Index [DLQI])

There is a statistically significant difference in favour of dupilumab for the proportion of patients in the relevant age stratum with a DLQI score of 0 or 1 at week 52. This resulted in a hint of an added benefit of dupilumab in comparison with the comparator therapy.

Side effects - specific adverse events (AEs)

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

At week 52, there was a statistically significant difference to the disadvantage of dupilumab versus the comparator therapy compared to baseline. This resulted in a hint 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, the overall assessment yields positive effects in the outcome categories “morbidity” and “health-related quality of life”

[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

for the target population of children aged 6 to 11 years with severe atopic dermatitis who are candidates for systemic therapy. These positive effects were also shown for patients of the target population in study AD-1652 after 16 weeks, which was presented as supplementary information.

In the relevant age stratum, there is a negative effect in the outcome category "side effects", which is caused by the outcome "eye disorders". This negative effect is not shown in study AD-1652 with patients of the target population presented as supplementary information. Overall, the negative effect in the outcome "eye disorders" in the relevant age stratum of the CHRONOS study does not call into question 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.

In summary, this results in a hint of a non-quantifiable added benefit of dupilumab in comparison with the ACT for children 6 to 11 years of age with severe atopic dermatitis who are candidates for systemic therapy.

Table 3 shows a summary of 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]**
Children 6 to 11 years of age with severe atopic dermatitis who are candidates for systemic therapy	An individually optimized treatment regimen depending on the extent of the disease and taking the prior therapy into account, under consideration of the following treatments: ▪ topical class 2 to 3 glucocorticoids ▪ tacrolimus (topical)	Hint of 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. In addition to the treatment of relapses, it should also be possible to adjust the therapy in the chronic phases of the study. Systemic glucocorticoids may be indicated in children as part of short-term relapse treatment.
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 children 6 to 11 years of age.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

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].

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 was to assess the added benefit of dupilumab in comparison with the ACT in children 6 to 11 years of age with severe atopic dermatitis who are candidates for systemic therapy.

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]**
Children 6 to 11 years of age with severe atopic dermatitis who are candidates for systemic therapy	An individually optimized treatment regimen depending on the extent of the disease and taking the prior therapy into account, under consideration of the following treatments: ▪ topical class 2 to 3 glucocorticoids ▪ tacrolimus (topical)
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). 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 flares was assumed and was to be differentiated from therapy adjustment during the chronic phases; however, the option of adjustment during the flares alone was not to be considered an individually optimized treatment regimen within the framework of the envisaged therapeutic indication. In addition to the treatment of flares, it should also be possible to adjust the therapy in the chronic phases of the study. Systemic glucocorticoids may be indicated in children as part of short-term relapse treatment.

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 conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum treatment duration of 24 weeks 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 study duration of 13 weeks for the target population of children from 6

to 11 years of age. Moreover, the company specified a minimum study duration of 24 weeks for patients aged ≥ 12 years. The company set this specification in order to meet the minimum study duration required by the G-BA and to transfer data on efficacy and safety from an older patient population to the target population of children aged 6 to 11 years as part of an evidence transfer.

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 October 2020)
- bibliographical literature search on dupilumab (last search on 22 October 2020)
- search in trial registries/trial results databases for studies on dupilumab (last search on 26 October 2020)
- search on the G-BA website for dupilumab (last search on 26 October 2020)

To check the completeness of the study pool:

- search in trial registries for studies on dupilumab (last search on 14 January 2021)

The check did not identify any additional relevant studies.

2.3.1 Studies included

The study presented 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			Available sources		
	Study for the approval of 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 and other sources[c] yes/no [citation])
R668-AD-1224 (CHRONOS[d,e])	No	Yes	No	No[f]	Yes [3-5]	Yes [6-11]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website; EPAR; medical review of the FDA.
d. In the following tables, the study is referred to with this abbreviated form.
e. The age stratum ≥ 18 to < 40 years was used for the derivation of the added benefit for children from 6 to 11 years of age.
f. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

EPAR: European Public Assessment Report; FDA: U. S. Food and Drug Administration; G-BA: Federal Joint Committee; RCT: randomized controlled trial; TCS: topical corticosteroids

b. In the present data constellation, the age stratum ≥ 18 to < 40 years of the CHRONOS study R668-AD-1224 (hereinafter referred to as CHRONOS study) was used for the benefit assessment of dupilumab in comparison with the ACT in children 6 to 11 years of age. The study is already known from dossier assessments A17-63 [8] and A19-75 [9] and the corresponding addendum A20-01 [1].

This deviates from the company's approach, which considered study R668-AD-1652 (hereinafter referred to as study AD-1652) [12-16] with children aged 6 to 11 years in addition to data from the CHRONOS study for its assessment of dupilumab in the present therapeutic indication. The company used the data of the total population of the CHRONOS study to transfer its results to the target population of children aged 6 to 11 years, as the AD-1652 study has a treatment duration of 16 weeks and therefore does not meet the minimum treatment duration of 24 weeks required in the present therapeutic indication.

In the present data constellation, the AD-1652 study can be used to investigate the transferability of the results from adults to children 6 to 11 years of age (see below).

Study AD-1652 unsuitable for the assessment of the added benefit

Study AD-1652 presented by the company was unsuitable for assessing the added benefit of dupilumab versus the ACT. The AD-1652 study is first described, followed by a justification of its lack of suitability for the assessment of the added benefit.

Study characteristics

Study design

AD-1652 is a randomized, double-blind, controlled study on the comparison of dupilumab (in different dosages and dosing intervals) with placebo. The treatment duration was 16 weeks. The planned follow-up observation period for the individual outcomes was 12 weeks. Alternatively, patients had the opportunity to participate in the open, single-arm study AD-1434.

The study included patients between 6 and < 12 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. Inadequate response was defined as not achieving and not maintaining remission or lower disease activity (Investigator's Global Assessment [IGA 0-2] despite daily treatment with moderate-potency to high-potency TCS with or without topical calcineurin inhibitors (TCI) for at least 28 days. 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 ≥ 15%, Eczema Area and Severity Index (EASI) ≥ 21 and IGA = 4. For the present benefit assessment, this definition of the severity grade was regarded as adequate representation of the severe atopic dermatitis.

Patients were randomized according to body weight at baseline (< 30 kg vs. ≥ 30 kg) and region (North America vs. Europe). All of the 367 patients of the study were randomly assigned (1:1:1) to subcutaneous treatment with dupilumab once every 2 weeks (A), dupilumab once every 4 weeks (B) or placebo once every 2 or 4 weeks (C).

Patients in study arm A (N = 122) received dupilumab at a dose of 100 mg for body weights ≥ 15 and < 30 kg or 200 mg for body weights ≥ 30 kg. The dosage of 100 mg dupilumab once every 2 weeks is not approved in Germany. According to the Summary of Product Characteristics (SPC), the dosing regimen of 200 mg dupilumab every 2 weeks is an escalation option at the physician’s discretion for body weights between 15 and < 60 kg based on the dose of 300 mg every 4 weeks in compliance with the approval [17,18]. The dosage of 200 mg dupilumab every 2 weeks represents no approval-compliant dosage at the start of treatment. Treatment arm A is therefore not considered further.

In study arm B (N = 122), dupilumab was administered once every 4 weeks at a dose of 300 mg regardless of body weight. Deviating from the SPC, children with body weights ≥ 60 kg also received 300 mg dupilumab every 4 weeks. However, according to the SPC [17,18], children with body weights ≥ 60 kg are to receive 300 mg dupilumab at 2-week intervals. Study AD-1652 included a total of 10 children with body weights ≥ 60 kg, although it is unclear whether and how many of them were assigned to the 300 mg dupilumab arm and thus received no approval-compliant treatment. Overall, the company did not consider children ≥ 60 kg in its analyses. Another deviation from the SPC results from the administration of an initial dose of

600 mg on day 1. According to the SPC, the initial dose is to be administered in the form of 2 doses of 300 mg each on day 1 and day 15 [17,18].

Patients in study arm C (N = 123) received placebo once every 2 weeks or every 4 weeks, according to random allocation (1:1) within the two weight strata (< 30 kg and ≥ 30 kg). In Module 4 E, the company only presented results of those children in the placebo arm who received placebo every 4 weeks (N = 59), with the justification that this control group reflected the approval-compliant treatment regimen.

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. 14 days prior to initiation of treatment with the study medication, standardized background therapy with moderate-potency TCS was initiated on skin areas with active lesions. At the physician's discretion, mild-potency TCS could be applied to areas with thin skin once daily (e.g. skin, face, genital area) or to areas where permanent treatment with moderate-potency TCS is considered unsafe. Topical treatment with tacrolimus was not allowed during treatment with the study medication. With an IGA ≤ 2, the use of moderate-potency TCS was reduced to 3 times per week. If the skin was free of lesions (corresponding to an IGA = 0), the TCS were discontinued. Reoccurrence of lesions entailed the reinitiation of treatment with moderate-potency TCS. With an IGA = 4 or intolerable symptoms under treatment with moderate-potency TCS once daily, the therapy could be escalated.

Treatment escalation with high-potency TCS (once daily each), systemic glucocorticoids as well as systemic non-steroidal immunosuppressants were referred to as rescue therapy in study AD-1652. According to the study documents, these therapies were only permitted as rescue therapies, but are listed in Module 4 E of the dossier (Section 4.3.1.2.1 of the full dossier assessment) predominantly as concomitant medication, which is why this information is referred to below. If possible, the first escalation had to be performed with high-potency TCS. Only patients who had not shown adequate improvement after topical therapy for at least 7 days were to receive systemic therapies. Treatment with systemic therapies led to permanent discontinuation of the study medication. Overall, only few children received treatment with systemic glucocorticoids or systemic non-steroidal immunosuppressants (1 in 118 children in the dupilumab arm and 6 in 59 children in the placebo arm). 51 of 118 children (43%) in the dupilumab arm and 27 of 59 children (46%) in the placebo arm received therapy escalation with high-potency TCS.

The following limitations exist with regard to the ACT in the AD-1652 study:

- Individual decisions on which therapy would have been optimal for each patient on study entry were not planned in the study. It is conceivable that treatment with high-potency topical or systemic therapies (as part of a short-term relapse treatment) would have been the individually optimized treatment for some patients at the start of the study.

- Topical treatment with tacrolimus as part of the G-BA's ACT was not permitted during treatment with the study medication. Only 3 patients (out of 118) in the intervention arm received a therapy not belonging to the TCS, which included TCI (e.g. tacrolimus) among other substances. The study documents provide no information on the extent to which tacrolimus would have presented the individually optimized treatment for further patients.
- 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, affected skin areas were treated with topical therapies also after the skin changes had subsided (intermittent subsequent treatment; once to twice weekly) [19-21]. The TCS background therapy used in AD-1652 with the option of rescue therapy in the event of non-response or intolerable symptoms represents a therapy regimen in the sense of a reactive therapy approach. In the dupilumab arm, continuous administration of dupilumab (once every 4 weeks) is assessed as therapy strategy comparable with the proactive treatment approach also in case of lesion-free or almost lesion-free skin textures. However, the option of a proactive treatment approach was not available to the patients in the comparator arm. Given the missing option of a proactive treatment approach in lesion-free periods, the options of an individually optimized treatment regimen depending on the disease and under consideration of the previous treatment were not completely exhausted in the comparator arm. 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.

The described limitations of the AD-1652 study remain without consequence for the present benefit assessment, as the treatment duration was too short to assess the added benefit of dupilumab compared to the ACT (see below).

Study duration too short to assess long-term effects of dupilumab on the chronic-inflammatory course of atopic dermatitis

The treatment duration of AD-1652 used by the company was 16 weeks. Thus, the AD-1652 study does not fulfil the minimum treatment duration of 24 weeks in the present therapeutic indication. The company refers to the comments of the Ethics Committee of the German Medical Association [22] and to the information sheet of the Federal Ministry of Health (BMG), the Federal Institute for Drugs and Medical Devices (BfArM) and the Paul Ehrlich Institute (PEI) [23], which only advocate studies in children and adolescents if the research question cannot be adequately answered by comparable studies in adults. Since an extensive study programme with RCTs is available for adults, the company considered a treatment duration of 16 weeks to be sufficient for the derivation of an added benefit for children aged 6 to 11 years. The company states that long-term data from the RCT CHRONOS with adults should additionally be used for the early benefit assessment in order to meet the requirement of a presentation of results over 24 weeks for this patient group, which applies to chronic diseases.

In addition to the AD-1652 study, the company therefore also used results from the CHRONOS study with adults with moderate to severe atopic dermatitis at week 52 in order to transfer these results to the target population of children aged 6 to 11 years with severe atopic dermatitis (see above).

Due to the chronic-inflammatory course of atopic dermatitis, a minimum study duration of 24 weeks is required for the early benefit assessment, as the permanent control of the disease and the long-term prevention of relapses are central therapy goals, especially for the target population of children aged 6 to 11 years with severe atopic dermatitis. The G-BA also considers a treatment duration of 24 weeks to be required as a rule and a treatment duration of 52 weeks to be desirable in the present therapeutic indication.

With a treatment duration of 16 weeks, the AD-1652 study is overall too short to assess long-term effects of dupilumab on the chronic-inflammatory course of atopic dermatitis. However, the study can be used to investigate the transferability of the results of the CHRONOS study to children aged 6 to 11 years (see below). The study and intervention characteristics of study AD-1652 are presented in Table 13 and Table 14 in Appendix A of the full dossier assessment.

Study CHRONOS

The CHRONOS study was already used in dossier assessments A17-63 [8] and A19-75 [9] as well as in the corresponding addendum A20-01 [10] for the assessment of the added benefit of dupilumab versus the ACT in adults and adolescents with moderate to severe atopic dermatitis who are candidates for systemic therapy. 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[4] (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 background therapy with moderate-potency TCS, which could be discontinued or reinitiated as required for each individual patient. 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 [8] for a detailed description of the study and intervention characteristics of the already known CHRONOS study.

[4] "A dosage of 300 mg once weekly is not approved in Germany and is thus not further considered in the present benefit assessment."

Transfer of the results of the age stratum ≥ 18 to < 40 years to children aged 6 to 11 years

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 RCT AD-1652 are available for children aged 6 to 11 years with 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 the treatment duration was not long enough to draw conclusions on the added benefit of long-term administration of dupilumab in atopic dermatitis.

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

- Pathogenesis and clinical picture of children from 6 to 11 years and adults are sufficiently similar in the therapeutic indication of atopic dermatitis [20,24,25].
- In the CHRONOS study, no significant effect modification by age and severity of the disease was observed.
- Overall, the AD-1652 study showed consistent and large effects across the different outcomes at week 16, both within the CHRONOS study and compared to it at week 24 [9] and week 52.

In terms of disease severity, the approved therapeutic indication of dupilumab differs between adults (moderate to severe atopic dermatitis) and children aged 6 to 11 years (severe atopic dermatitis). The youngest age stratum (≥ 18 to < 40 years) of the CHRONOS study with severe atopic dermatitis is the best possible approximation to the target population. However, the company presented no analyses on this subpopulation.

In the present situation, the age stratum ≥ 18 to < 40 years of the CHRONOS study is considered for the assessment, which includes both patients with severe and moderate atopic dermatitis. According to the classification of the severity grades based on EASI [26] or SCORAD [21], most patients in the total population and the relevant age stratum of the CHRONOS study had severe forms of the disease (> 80 %) according to Institute's calculation based on mean values and standard deviations under assumption of a normal distribution. According to the classification of the severity grades based on IGA [27], moderate (IGA = 3) and severe (IGA = 4) forms of disease were almost equally represented in both treatment groups. As the CHRONOS study did not show any significant effect modification by disease severity (see Section 2.4.4), the transfer of the results of the age stratum ≥ 18 to < 40 years with moderate to severe atopic dermatitis of the CHRONOS study to the target population of children 6 to 11 years with severe atopic dermatitis is not called into question. The results of the total population are presented as supplementary information in the present benefit assessment.

The age stratum ≥ 18 to < 40 years of the CHRONOS study comprised 52 patients in the relevant intervention arm and 189 patients in the comparator arm. The results at week 52 were used. The outcomes that presented the basis for the conclusion of dossier assessment A17-63 [8] and the decision on the procedure of dupilumab in adult patients [28,29] served as a basis for the transfer. The patient characteristics of the age stratum ≥ 18 to < 40 years are presented in Table 15 in Appendix B of the full dossier assessment; they are particularly comparable to those of the total population with regard to the disease severity at baseline. Information on prior therapies for the relevant age stratum was submitted by the company in the commenting procedure on the benefit assessment of dupilumab in the adolescent target population (Commission A19-75) and already presented in the corresponding addendum A20-01 [10]. For patient characteristics and prior therapies of the overall population, see dossier assessment A17-63 [8].

The results of study AD-1652 on the outcomes of dossier assessment A17-63 used in the present benefit assessment are presented as supplementary information in Appendix C 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. The proportion of patients who had discontinued treatment in the relevant age stratum until week 52 was 11.5% (6 of 52 patients) in the relevant dupilumab arm and 31.2% (59 of 189 patients) in the comparator arm [10]. It remains unclear whether background therapy was continued for these patients.

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

A detailed presentation of the limitations of the CHRONOS study can be found in dossier assessment A17-63 [8].

Summary

The age stratum ≥ 18 to < 40 years with moderate to severe atopic dermatitis of the CHRONOS study was used for the assessment of the added benefit of dupilumab in comparison with the

ACT in children aged 6 years to 11 years with severe atopic dermatitis for whom systemic therapy is an option. The AD-1652 study was unsuitable for the derivation of an added benefit in comparison with the ACT. The results of AD-1652 are presented as supplementary information in Appendix C of the full dossier assessment.

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 the 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 (narrow Customized Medical Dictionary for Regulatory Activities [MedDRA] Query [CMQ])

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes.

Note on types of analysis and data cut-off

For the derivation of the added benefit, the company used the total population of the CHRONOS study in order to transfer its results to the paediatric target population. According to the statements of the company, the types of analysis considered adequate in dossier assessment A19-75 [9] were used for this purpose.

In Section 4.2.5.2.1.1 of Module 4 E of the full dossier assessment, the company states that it used the prespecified sensitivity analysis for dichotomous efficacy outcomes, which - irrespective of the implementation of a rescue therapy - was based on the values actually observed, and that this was combined with the prespecified sensitivity analysis, in which missing values were imputed using the “last observation carried forward (LOCF)” strategy.

For continuous outcomes, the company explained to use the sensitivity analysis, which - independent of the implementation of rescue therapy - is based on the actually observed values and, in addition, replaces missing values by means of multiple imputation (MI).

The company did not explicitly name the data cut-off on which it based its conclusions on the added benefit. It can be assumed that the company used the final, second data cut-off (16 December 2016). The data cut-off was conducted after all patients had achieved week 52.

Although it is assumed that the company, in accordance with its explanations, chose the types of analysis for continuous outcomes that were also used in dossier assessment A17-63, and that the results presented in Module 4 E are based on the final data cut-off of the CHRONOS study, the values achieved for the total population presented as supplementary information deviate numerically from the results presented in A17-63 (see Section 2.4.3). However, as these deviations did not result in a qualitatively different statement, the data on the total population reported in Module 4 E of the dossier were presented for the present benefit assessment.

For the dichotomous outcomes, the deviations from the results presented in A17-63 can be explained by the different type of analysis (LOCF replacement).

2.4.2 Risk of bias

See dossier assessment A17-63 [8] for the assessment of the risk of bias across outcomes of the CHRONOS study.

Analogous to the procedure in A20-01 [10], the risk of bias was rated as high for all results of the outcomes included in the present benefit assessment for patients in the age stratum ≥ 18 to < 40 years.

Transferability of the study results to the German health care context

Taking into account the approval of dupilumab valid in Germany, the locations where the study was conducted, the patient characteristics (family origin and demographic parameters) and the prior and rescue therapies administered, the company considers the results of the AD-1652 study to be transferable to the German healthcare context. As described in Section 2.3.1, the AD-1652 study is unsuitable for answering the research question of the present benefit assessment.

The company considers the transferability of the results of the CHRONOS study to the German health care context to be already confirmed in the benefit assessment of adults.

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

2.4.3 Results

Table 6 and Table 7 summarize the results on the comparison of dupilumab + TCS with placebo + TCS at week 52 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.

Appendix D of the full dossier assessment presents the results on the outcomes EASI 75, EASI 90, SCORAD 75 and SCORAD 90 as supplementary information each for the age stratum ≥ 18 to < 40 years and for the total population of the CHRONOS study at week 52.

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

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**
CHRONOS (week 52)[a]					
Morbidity					
Symptoms					
Itching – peak pruritus NRS (improvement by ≥ 4 points)[b]					
Stratum ≥ 18 to < 40 years	50	31 (62.0)	182	59 (32.4)	1.86 [1.37; 2.53]; < 0.001[c]
Total population (supplementary information)	*102*	*66 (64.7)*	*299*	*99 (33.1)*	*1.94 [1.57; 2.40]; < 0.001[c]*
Health-related quality of life					
DLQI (0 or 1)					
Stratum ≥ 18 to < 40 years	52	23 (44.2)	189	30 (15.9)	2.64 [1.69; 4.12]; < 0.001[c]
Total population (supplementary information)	*106*	*45 (42.5)*	*315*	*53 (16.8)*	*2.55 [1.84; 3.55]; < 0.001[c]*
Side effects					
Eye disorders (SOC, AEs)					
Stratum ≥ 18 to < 40 years	55	17 (30.9)	189	22 (11.6)	2.66 [1.52; 4.65]; < 0.001
Total population (supplementary information)	*110*	*33 (30.0)*	*315*	*43 (13.7)*	*2.20 [1.47; 3.28]; < 0.001*
Supplementary: conjunctivitis (narrow CMQ)[d]					
Stratum ≥ 18 to < 40 years				ND	
Total population (supplementary information)[e]	*110*	*15 (13.6)*	*315*	*25 (7.9)*	*1.72 [0.94; 3.14]; 0.079[f]*

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

Study outcome category outcome	Dupilumab + TCS N	Dupilumab + TCS patients with event n (%)	Placebo + TCS N	Placebo + TCS patients with event n (%)	Dupilumab + TCS vs. placebo + TCS RR [95% CI]; p-value
a. In some cases, the data of the present dossier lead to numerically deviating values compared to A17-63 (total population) or A20-01 (stratum ≥ 18 to < 40 years), which, however, do not result in a qualitatively deviating statement. Unless stated otherwise, the values reported in Module 4 E of the dossier are presented. b. The response criterion ≥ 4 points was predefined and corresponds to ≥ 15% of the scale range. Thus, as explained in the General Methods of the Institute [1,30], the response criterion reflects a noticeable change for patients in a sufficiently reliable manner. c. Logistic regression model, adjusted for randomization strata. d. Post hoc operationalization on conjunctivitis with 5 PTs (conjunctivitis [narrow CMQ]: conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, atopic keratoconjunctivitis). The examination on conjunctivitis events is based on the increased occurrence of conjunctivitis as well as further selected eye diseases under treatment with dupilumab. e. The data presented are from the medical review of the FDA [6]. f. Institute's calculation: 95% CI asymptotic; unconditional exact test, (CSZ method according to [31]).					
CI: confidence interval; CMQ: Customized MedDRA Query; DLQI: Dermatology Life Quality Index; FDA: U. S. Food and Drug Administration; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; NRS: numeric rating scale; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SOC: System Organ Class; TCS: topical corticosteroids					

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

Study outcome category outcome	Dupilumab + TCS			Placebo + TCS			Dupilumab + TCS vs. placebo + TCS
	N[a]	values at baseline mean (SD)	change at week 52 mean[b] (SE)	N[a]	values at baseline mean (SD)	change at week 52 mean[b] (SE)	MD [95% CI]; p-value[b]
CHRONOS (week 52)[c]							
Morbidity							
Symptoms							
Patient-reported symptoms – POEM[d]							
Stratum ≥ 18 to < 40 years	52	20.5 (5.15)	-12.5 (0.94)	189	20.4 (6.00)	-7.1 (0.52)	-5.5 [-7.54; -3.41]; < 0.001 Hedges' g: −0.85 [−1.16; −0.53]
Total population (supplementary information)	*106*	*20.3 (5.68)*	*-13.8 (0.66)*	*314*	*20.0 (5.98)*	*-6.7 (0.40)*	*-7.0 [-8.51; -5.57]; < 0.001* *Hedges' g: −1.08 [−1.30; −0.85]*
Insomnia - SCORAD VAS[d]							
Stratum ≥ 18 to < 40 years	52	5.4 (3.31)	-4.1 (0.27)	189	4.9 (3.22)	-2.9 (0.14)	-1.2 [-1.75; -0.59]; < 0.001 Hedges' g: −0.65 [−0.97; −0.33]
Total population (supplementary information)	*105*	*5.6 (3.15)*	*-4.0 (0.19)*	*313*	*4.9 (3.26)*	*-2.9 (0.12)*	*-1.1 [-1.56; -0.69]; < 0.001* *Hedges' g: −0.59 [−0.82; −0.36]*
Health status							
EQ-5D VAS[e]							
Stratum ≥ 18 to < 40 years	52	58.4 (22.10)	20.1 (2.26)	189	55.2 (22.87)	15.4 (1.25)	4.7 [-0.28; 9.64]; 0.064
Total population (supplementary information)	*105*	*57.8 (22.52)*	*21.4 (1.65)*	*314*	*56.5 (23.67)*	*15.2 (0.97)*	*6.2 [2.46; 9.85]; 0.001* *Hedges' g: 0.38 [0.15; 0.61]*

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b. ANCOVA model with baseline values, treatment arm and randomization strata as covariates.
c. In some cases, the data of the present dossier lead to numerically deviating values compared to A17-63 (total population) or A20-01 (stratum ≥ 18 to < 40 years), which, however, do not result in a qualitatively deviating statement. The values reported in Module 4 E of the dossier are presented.
d. Lower (decreasing) values indicate better symptoms; negative effects (intervention minus control) indicate an advantage for the intervention.
e. Higher (increasing) values indicate better health status; positive effects (intervention minus control) indicate an advantage for the intervention.

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

Study outcome category outcome	Dupilumab + TCS			Placebo + TCS			Dupilumab + TCS vs. placebo + TCS
	N[a]	values at baseline mean (SD)	change at week 52 mean[b] (SE)	N[a]	values at baseline mean (SD)	change at week 52 mean[b] (SE)	MD [95% CI]; p-value[b]
ANCOVA: analysis of covariance; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions Assessment; MD: mean difference; N: number of analysed patients; POEM: Patient-Oriented Eczema Measure; RCT: randomized controlled trial; SCORAD: SCORing Atopic Dermatitis; SD: standard deviation; SE: standard error; TCS: topical corticosteroids; VAS: visual analogue scale							

As described in Section 2.3.1, the results of the age stratum ≥ 18 to < 40 years with moderate to severe atopic dermatitis from the CHRONOS study are used to draw conclusions on the added benefit of dupilumab in children aged 6 to 11 years with severe atopic dermatitis.

On the basis of the available data, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Morbidity

Symptoms (itching – Peak Pruritus NRS)

For the symptom outcome "itching (Peak Pruritus NRS)", responder analyses for an improvement ≥ 4 points at week 52 were used. 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. This resulted in a hint of an added benefit of dupilumab versus the comparator therapy.

This deviates from the company's assessment, which derived an indication of an added benefit across all outcomes of the category "morbidity" based on the results for the total population of the CHRONOS study and the results of the AD-1652 study.

In the commenting procedure on benefit assessment A19-75, the company submitted the documents for the classification of the severity of the itching [32]. According to this, severe itching commences at a value of 7. Since the mean baseline value of the peak pruritus NRS of the patients in the relevant age stratum of the CHRONOS study was 7.6 (dupilumab arm) and 7.4 (comparator arm) at the start of the study (see Table 15 in Appendix B of the full dossier assessment), the outcome "itching (peak pruritus NRS)" was assigned to the outcome category "serious/severe symptoms/late complications" analogous to the assessment in A20-01 [10] in the present assessment.

Patient-reported symptoms (POEM)

For patient-reported symptoms recorded using POEM, the mean change at week 52 compared to baseline was considered. 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 standardized mean difference (SMD) in the form of Hedges' g was considered to check the relevance of the result. For the relevant age stratum and the total population, 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 a hint of an added benefit of dupilumab versus the comparator therapy.

This deviates from the company' s approach, which derived an indication of an added benefit across all outcomes of the category "morbidity" based on the results for the total population of the CHRONOS study and the results of the AD-1652 study.

Analogous to the assessment in A17-63 [8], A19-75 [9] und A20-01 [10] , 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 52 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. For the relevant age stratum and the total population, the 95% CI the SMD was completely below the irrelevance threshold of –0.2. This was interpreted to be a relevant effect. This resulted in a hint of an added benefit of dupilumab versus the comparator therapy.

This deviates from the company's assessment, which derived an indication of an added benefit across all outcomes of the category "morbidity" based on the results for the total population of the CHRONOS study and the results of the AD-1652 study.

Analogous to the assessment in A17-63 [8] and A20-01 [10], the outcome "insomnia (SCORAD VAS)" was assigned to the outcome category "non-serious/non-severe symptoms/late complications".

Health status (EQ-5D VAS)

For the outcome "health status", recorded using the EQ-5D VAS, no statistically significant difference between the treatment groups was shown for the relevant age stratum for the mean change at week 52 compared to baseline. A statistically significant difference in favour of dupilumab was shown for the total population presented as supplementary information. The SMD in the form of Hedges' g was considered to check the relevance of the result. The 95% CI of the SMD was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant in the total population. 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.

This deviates from the company's assessment, which derived an indication of an added benefit across all outcomes of the category "morbidity" based on the results for the total population of the CHRONOS study and the results of the AD-1652 study.

Health-related quality of life

DLQI

There is a statistically significant difference in favour of dupilumab for the proportion of patients in the relevant age stratum with a DLQI score of 0 or 1 at week 52. This effect was also shown for the total population presented as supplementary information. This resulted in a hint of an added benefit of dupilumab in comparison with the comparator therapy.

This differs from the company's assessment, which used further operationalizations and derived an indication of an added benefit based on the results of the total population of the CHRONOS study and the results of the AD-1652 study.

Side effects

Specific AEs

Eye disorders (SOC, AE)

At week 52, a statistically significant difference to the disadvantage of dupilumab versus the comparator therapy was shown for the outcome "eye disorders" in the relevant age stratum. This effect was also shown for the total population presented as supplementary information.

Moreover, the present benefit assessment additionally considered the narrow CMQ query "conjunctivitis". This outcome comprises 5 preferred terms (PTs) that represent the AE "conjunctivitis" more comprehensively than the SOC "eye disorders". The PTs "conjunctivitis", "bacterial conjunctivitis" and "viral conjunctivitis", for instance, which were not included in the SOC "eye disorders", were comprised in the operationalization "conjunctivitis (narrow CMQ)". In the AD-1652 study, the recording of conjunctivitis was pre-specified within a narrow Standardized MedDRA Query (SMQ) and included the same PTs as the narrow CMQ in the CHRONOS study. The narrow CMQ was analysed post hoc in the CHRONOS study, since an increased incidence of conjunctivitis was observed in previous phase 3 studies under treatment with dupilumab.

For the outcome "conjunctivitis (narrow CMQ)", no data are available for the relevant age stratum ≥ 18 to < 40 years of the CHRONOS study. For the outcome "conjunctivitis (narrow CMQ)", the results for the total population at week 52 presented as supplementary information show no statistically significant difference between the treatment arms.

Overall, this resulted in a hint of greater harm from dupilumab in comparison with the comparator therapy for the outcome "eye disorders (SOC)".

This deviates from the company's assessment, which derived no greater or lesser benefit across all safety outcomes based on the results for the total population of the CHRONOS study and the results of the AD-1652 study.

2.4.4 Subgroups and other effect modifiers

See dossier assessment A17-63 [8] for the selection of subgroups and other effect modifiers for the CHRONOS study. No subgroup analyses are available for the relevant age stratum ≥ 18 to < 40 years.

The subgroup analyses for the total population were additionally considered. Module 4 E of the dossier does not explicitly state on which data cut-off of the CHRONOS study the company based its subgroup analyses. However, it can be assumed that the company based its analyses on the final second data cut-off (16 December 2016) (see also Section 2.4.1). Thus, the analyses are based on a different data cut-off than in dossier assessment A17-63.

For the total population of the CHRONOS study, an effect modification was found at week 52 for the characteristic "age" for the outcome "EASI 90" presented as supplementary information in Appendix D ($p = 0.0161$). This effect modification 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 52, 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 stratum ≥ 18 to < 40 years to the target population of children 6 to 11 years was thus not called into question.

In addition, interactions were observed for the characteristic "disease severity (IGA = 3 vs. IGA = 4)" for 2 outcomes. An interaction ($p = 0.0425$) suggesting an increase of the effect towards a lower severity of the atopic dermatitis was found for the outcome "peak pruritus NRS (improvement by ≥ 4 points)". However, the effects were in the same direction and there was a statistically significant difference in favour of dupilumab independent of the severity. An interaction ($p < 0.0001$) suggesting an increase of the effect towards a higher severity of atopic dermatitis was also found for the outcome "EASI 75" presented as supplementary information in Appendix D of the full dossier assessment. Here again, the effects were in the same direction. Despite these interactions, there was no significant effect modification by severity of the disease across the considered outcomes for the CHRONOS study at week 52.

Overall, there are consistent and large effects across the different outcomes (see Section 2.4.3). This does not call into question the transfer of the results of the CHRONOS study to the target population of children aged 6 to 11 years with severe atopic dermatitis. For the best possible approximation to the target population of children aged 6 to 11 years with severe atopic dermatitis in the present data situation, the age stratum ≥ 18 to < 40 years with moderate to severe atopic dermatitis of the CHRONOS study was used in the present benefit assessment (see Section 2.3.1).

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below. Taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *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.

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 "serious/severe symptoms/late complications": ▪ itching (Peak Pruritus NRS): hint of an added benefit – extent: "major" outcome category "non-serious/non-severe symptoms/late complications": ▪ patient-reported symptoms (POEM): hint of an added benefit – extent: non-quantifiable ▪ insomnia (SCORAD-VAS): hint of an added benefit – extent: "non-quantifiable"	Outcome category: non-serious/non-severe side effects: ▪ eye disorders: hint of greater harm – extent: "considerable"
Outcome category "health-related quality of life": ▪ DLQI (0 or 1): hint of an added benefit – extent: "major"	-
a. 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 children 6 to 11 years of age. DLQI: Dermatology Life Quality Index; NRS: Numerical Rating Scale; POEM: Patient-Oriented Eczema Measure; SCORAD: SCORing Atopic Dermatitis; TCS: topical glucocorticoids; VAS: visual analogue scale	

Based on the age stratum ≥ 18 to < 40 years of the CHRONOS study, the overall assessment yields positive effects in the outcome categories "morbidity" and "health-related quality of life" for the target population of children aged 6 to 11 years with severe atopic dermatitis who are candidates for systemic therapy. These positive effects were also shown for patients of the target population in study AD-1652 after 16 weeks, which was presented as supplementary information.

In the relevant age stratum, there is a negative effect in the outcome category "side effects", which is caused by the outcome "eye disorders". This negative effect is not shown in study AD-1652 with patients of the target population presented as supplementary information. Overall, the negative effect in the outcome "eye disorders" in the relevant age stratum of the CHRONOS study does not call into question 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; this classification is maintained for the relevant age stratum in the present benefit assessment.

In summary, this results in an hint of a non-quantifiable added benefit of dupilumab in comparison with the ACT for children 6 to 11 years of age with severe atopic dermatitis who are candidates for systemic therapy.

The result of the assessment of the added benefit of dupilumab in comparison with the ACT is summarized in Table 9.

Table 9: Dupilumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit[b]**
Children 6 to 11 years of age with severe atopic dermatitis who are candidates for systemic therapy	An individually optimized treatment regimen depending on the extent of the disease and taking the prior therapy into account, under consideration of the following treatments: ▪ topical class 2 to 3 glucocorticoids ▪ tacrolimus (topical)	Hint of 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. In addition to the treatment of relapses, it should also be possible to adjust the therapy in the chronic phases of the study. Systemic glucocorticoids may be indicated in children as part of short-term relapse treatment.
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 children 6 to 11 years of age.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company. Based on the results of the AD-1652 study and the total population of the CHRONOS study, which it transfers to the paediatric target population, the company derived an indication of considerable added benefit.

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.

1. Institute for Quality and Efficiency in Health Care. General methods 6.0 (German version) [online]. 2020 [Accessed: 27.01.2021]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Regeneron Pharmaceuticals. Study to Assess the Efficacy and Long-term Safety of Dupilumab (REGN668/SAR231893) in Adult Participants With Moderate-to-Severe Atopic Dermatitis (CHRONOS) [online]. 2017 [Accessed: 25.01.2021]. URL: https://ClinicalTrials.gov/show/NCT02260986.

4. Regeneron Pharmaceuticals. A Randomized, Double-Blind, Placebo-Controlled Study to Demonstrate the Efficacy and Long-Term Safety of Dupilumab in Adult Patients with Moderate-to-Severe Atopic Dermatitis [online]. [Accessed: 25.01.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-003254-24.

5. Regeneron Pharmaceuticals. A Randomized, Double-Blind, Placebo-Controlled Study to Demonstrate the Efficacy and Long-Term Safety of Dupilumab in Adult Patients With Moderate-to-Severe Atopic Dermatitis - ClinicalTrials.gov Study Results [online]. 2017. URL: https://clinicaltrials.gov/ct2/show/results/NCT02260986?view=results.

6. Food and Drug Administration. Dupixent; application number 761055Orig1s000; medical review [online]. 2017 [Accessed: 12.01.2021]. URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761055Orig1s000MedR.pdf.

7. European Medicines Agency. Dupixent: Assessment Report [online]. 2017 [Accessed: 12.01.2021]. URL: https://www.ema.europa.eu/documents/assessment-report/dupixent-epar-public-assessment-report_en.pdf.

8. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dupilumab (atopische Dermatitis): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2018 [Accessed: 26.03.2018]. URL: https://www.iqwig.de/download/a17-63_dupilumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

9. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dupilumab (atopische Dermatitis bei Jugendlichen): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2019 [Accessed: 02.12.2019]. URL: https://www.iqwig.de/download/a19-75_dupilumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

10. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dupilumab (atopische Dermatitis bei Jugendlichen): Addendum zum Auftrag A19-75 [online]. 2020 [Accessed: 28.02.2020]. URL: https://www.iqwig.de/download/a20-01_dupilumab_addendum-zum-auftrag-a19-75_v1-0.pdf.

11. Blauvelt A, De Bruin-Weller M, Gooderham M 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. https://dx.doi.org/10.1016/S0140-6736(17)31191-1.

12. Paller AS, Siegfried EC, Thaçi D et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial. J Am Acad Dermatol 2020; 83(5): 1282-1293. https://dx.doi.org/10.1016/j.jaad.2020.06.054.

13. Regeneron Pharmaceuticals. Study to Investigate the Efficacy and Safety of Dupilumab Administered With Topical Corticosteroids (TCS) in Participants ≥6 to <12 Years With Severe Atopic Dermatitis (AD) [online]. 2020 [Accessed: 25.01.2021]. URL: https://ClinicalTrials.gov/show/NCT03345914.

14. Regeneron Pharmaceuticals. A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab administered concomitantly with topical corticosteroids in patients, ≥6 years to <12 years of Age, With Severe Atopic Dermatitis [online]. [Accessed: 25.01.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-004997-16.

15. European Medicines Agency. Dupixent: Extension of indication variation assessment report [online]. 2020 [Accessed: 25.01.2021]. URL: https://www.ema.europa.eu/documents/variation-report/dupixent-h-c-4390-ii-0027-epar-assessment-report-variation_en.pdf.

16. Sanofi-Aventis Deutschland. Dupilumab (Dupixent): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4 E; Behandlung von schwerer atopischer Dermatitis bei Kindern von 6 bis 11 Jahren, die für eine systemische Therapie in Betracht kommen [online]. 2020. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/637/#dossier.

17. Sanofi Genzyme. Dupixent 200 mg Injektionslösung in einer Fertigspritze; Dupixent 200 mg Injektionslösung im Fertigpen [online]. 2021 [Accessed: 16.02.2021]. URL: https://www.fachinfo.de.

18. Sanofi Genzyme. Dupixent 300 mg Injektionslösung in einer Fertigspritze, Dupixent 300 mg Injektionslösung im Fertigpen [online]. 2021 [Accessed: 16.02.2021]. URL: https://www.fachinfo.de.

19. Eichenfield LF, Tom WL, Berger TG et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol 2014; 71(1): 116-132. https://dx.doi.org/10.1016/j.jaad.2014.03.023.

20. Werfel T, Aberer W, Ahrens F et al. Leitlinie Neurodermitis [atopisches Ekzem; atopische Dermatitis]. J Dtsch Dermatol Ges 2016; 14(1): e1-75. https://dx.doi.org/10.1111/ddg.12884.

21. Wollenberg A, Barbarot S, Bieber T et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol 2018; 32(5): 657-682. https://dx.doi.org/10.1111/jdv.14891.

22. Zentrale Ethikkommission bei der Bundesärztekammer. Stellungnahme der Zentralen Kommission zur Wahrung ethischer Grundsätze in der Medizin und ihren Grenzgebieten (Zentrale Ethikkommission) bei der Bundesärztekammer zur Forschung mit Minderjährigen [online]. 2004 [Accessed: 21.08.2020]. URL: https://www.aerzteblatt.de/archiv/42111/Stellungnahme-der-Zentralen-Kommission-zur-Wahrung-ethischer-Grundsaetze-in-der-Medizin-und-ihren-Grenzgebieten-(Zentrale-Ethikkommission)-bei-der-Bundesaerztekammer-zur-Forschung-mit-Minderjaehrigen.

23. Bundesministerium für Gesundheit. Klinische Prüfungen: Sichere Arzneimittel für Kinder und Jugendliche [online]. 2017 [Accessed: 13.11.2020]. URL: https://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/kam/kam-sichereAM.pdf?__blob=publicationFile&v=2.

24. Akdis CA, Akdis M, Bieber T et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. J Allergy Clin Immunol 2006; 118: 152-169. https://dx.doi.org/10.1111/j.1398-9995.2006.01153.x.

25. Bieber T, D'Erme AM, Akdis CA et al. Clinical phenotypes and endophenotypes of atopic dermatitis: Where are we, and where should we go? J Allergy Clin Immunol 2017; 139(4S): 58-64. https://dx.doi.org/10.1016/j.jaci.2017.01.008.

26. Leshem YA, Hajar T, Hanifin JM et al. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. Br J Dermatol 2015; 172(5): 1353-1357. https://dx.doi.org/10.1111/bjd.13662.

27. Futamura M, Leshem YA, Thomas KS et al. A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: Many options, no standards. J Am Acad Dermatol 2016; 74(2): 288-294. https://dx.doi.org/10.1016/j.jaad.2015.09.062.

28. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Dupilumab [online]. 2018 [Accessed: 22.02.2021]. URL: https://www.g-ba.de/downloads/40-268-4986/2018-05-17_AM-RL-XII_Dupilumab_D-328_TrG.pdf.

29. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Dupilumab [online]. 2018 [Accessed: 22.02.2021]. URL: https://www.g-ba.de/downloads/39-261-3314/2018-05-17_AM-RL-XII_Dupilumab_D-328_BAnz.pdf.

30. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dokumentation und Würdigung der Anhörung zum Entwurf der Allgemeinen Methoden 6.0 [online]. 2020 [Accessed: 27.01.2021]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_dwa-entwurf-fuer-version-6-0_v1-0.pdf.

31. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

32. Reich A, Chatzigeorkidis E, Zeidler C et al. Tailoring the Cut-off Values of the Visual Analogue Scale and Numeric Rating Scale in Itch Assessment. Acta Derm Venereol 2017; 97(6): 759-760. https://dx.doi.org/10.2340/00015555-2642.

The full report (German version) is published under https://www.iqwig.de/en/projects/a20-123.html.