Dupilumab
(atopic dermatitis, 6 months to 5 years)

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

EXTRACT

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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

No advisor on medical and scientific questions was available for the present dossier assessment.

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

IQWiG employees involved in the dossier assessment

- Christina Keksel
- Lisa Junge
- Christopher Kunigkeit
- Prateek Mishra
- Katrin Nink
- Anke Schulz
- Dorothea Sow
- Pamela Wronski

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Part I: Benefit assessment

I Table of contents

Page

I List of tables[2]

Page

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
CMQ	Custom MedDRA Query
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IDQOL	Infants' Dermatitis Quality of Life Index
IGA	Investigator Global Assessment
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
NRS	numeric rating scale
oSCORAD	objective Scoring Atopic Dermatitis
POEM	Patient Oriented Eczema Measure
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SCORAD	Scoring Atopic Dermatitis
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SOC	System Organ Class
TCI	calcineurin inhibitor
TCS	topical corticosteroids
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 30 March 2023.

Research question

The aim of the present report is to assess the added benefit of dupilumab in comparison with the appropriate comparator therapy (ACT) in children 6 months to 5 years old with severe atopic dermatitis who are candidates for systemic therapy.

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

Table 2: Research question of the benefit assessment of dupilumab

Therapeutic indication	**ACT**[a]
Children with severe atopic dermatitis, 6 months to 5 years old, who are candidates for systemic therapy[b]	An individually optimized treatment regimen depending on the severity of the disease and taking into account the prior therapy, under consideration of the following treatments: ▪ topical corticosteroids of classes 2 to 3 ▪ tacrolimus (topical)
a. Presented is the ACT specified by the G-BA. Regarding the implementation of the ACT, the G-BA pointed out that it was assumed for the specified ACT that other, alternative drugs are used in case of intolerance, and that a placebo comparison alone does not correspond to the ACT. In addition, the G-BA pointed out that systemic corticosteroids may be indicated in the context of short-term flare therapy in children. b. As per approval, the therapeutic indication comprises patients who are candidates for systemic therapy. Children 6 months to 5 years old with severe atopic dermatitis who are candidates for continuous systemic therapy are considered for the purpose of determining the ACT because the drug dupilumab is to be administered as continuous therapy and therefore represents an option only for patients who are candidates for continuous systemic therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company principally followed the G-BA's specification of the ACT, but did not mention the G-BA's notes on the ACT.

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

PRESCHOOL study unsuitable for assessing added benefit

In addition to the R668-AD-1224 study (hereinafter referred to as "CHRONOS" study; see below), the company used the PRESCHOOL study for its assessment. The PRESCHOOL study is a 2-part study of dupilumab in patients aged 6 months to 5 years. Part A is not considered in the present benefit assessment. Part B is a randomized, double-blind, controlled study comparing dupilumab with placebo in children aged 6 months to 5 years with moderate to severe atopic dermatitis. In the study, a total of 162 patients were randomized in a 1:1 ratio to treatment with dupilumab (N = 83) or placebo (N = 79).

Lack of implementation of the appropriate comparator therapy

In the PRESCHOOL study, all children received a uniform background therapy with low-potency topical corticosteroids (TCS) at the beginning of the study; treatment escalation to medium or high-potency TCS or tacrolimus (topical) corresponding to the ACT, without permanent treatment discontinuation, was only allowed after day 14 and only in case of intolerable symptoms. The same applied to the use of systemic corticosteroids, whereby their use led to permanent treatment discontinuation.

According to various instruments for classifying severity, the majority of the patients had severe disease. For this reason, it is assumed that using only low-potency TCS at baseline was not sufficient for the patients in the comparator arm. In addition, using only class I TCS at baseline does not correspond to the ACT.

The ACT was also not adequately implemented during the course of the study. Thus, in the comparator arm, only 8 (10.1%) children received rescue therapy at week 2, and only 16 of 79 (20.3%) children at week 3. From week 12 to week 16, the proportion of patients with rescue therapy was 62% in the comparator arm. However, only 1 child (1.3%) at week 12, and only 4 out of 79 (5.1%) children at week 16 were lesion-free (Investigator Global Assessment [IGA] = 0) or almost lesion-free (IGA = 1). In addition, it is unclear how long the rescue therapy was administered to the individual children. Using only class I TCS in a relevant proportion of children with predominantly severe symptoms over the entire course of the study is therefore not appropriate and does not correspond to the ACT.

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

Due to the chronic-inflammatory course of atopic dermatitis, a minimum treatment 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 6 months to 5 years old 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 PRESCHOOL study is therefore overall too short to assess long-term effects of dupilumab on the chronic-inflammatory course of atopic dermatitis. However, the PRESCHOOL study can be used to investigate the transferability of the results of the CHRONOS study to children 6 months to 5 years old.

Transfer of the results of the age stratum ≥ 18 to < 40 years of the CHRONOS study to children 6 months to 5 years old

In addition to the PRESCHOOL study in children 6 months to 5 years of age, the 52-week CHRONOS study in adults with moderate to severe atopic dermatitis is available. In the present data constellation, the results of adults from the CHRONOS study can only be transferred to children whose clinical picture is sufficiently similar to that of adults. For children whose clinical picture is not sufficiently similar to that of adults, no conclusion on added benefit can be drawn on the basis of the available data. This is justified below.

The clinical picture of atopic dermatitis is heterogeneous overall. In particular, the clinical picture of early childhood atopic dermatitis differs from that of adults. About 1 to 2 years after disease onset, lichenified, chronic lesions dominate, especially flexural eczema with lichenification and dry scaling. These are characteristic of the clinical picture in adults.

Since the PRESCHOOL study included children from 6 months of age, the presence of atopic dermatitis that has become chronic was not an inclusion criterion. It can be assumed that the majority of the study population already had chronic atopic dermatitis or chronic lesions. However, there were also children with atopic dermatitis that had only been present for a short time (disease duration of 0 years), and whose disease had therefore not yet become chronic. Their proportion is unclear. The CHRONOS study, in contrast, only included adults with chronic atopic dermatitis.

The effects of differences in chronification and localization of the disease in the 2 patient populations are unclear. For this reason, in the present data constellation, a transfer is only possible to those children whose clinical picture is sufficiently similar to that of adults.

In addition, in the present data constellation, the following characteristics of the CHRONOS and PRESCHOOL studies support the transferability of the results of adults from the CHRONOS study to those children whose clinical picture is sufficiently similar to that of adults:

- In the CHRONOS study, no important effect modification by age and severity of the disease was observed.
- Overall, the PRESCHOOL study showed consistent and large effects across the different outcomes at week 16, both within the study and in comparison with the CHRONOS study at week 24 and week 52, as well as in comparison with the studies AD-1526 in 12 to < 18-year-olds and AD-1652 in 6 to < 12-year-olds (each at week 16).

For an approximation to the target population, the age stratum ≥ 18 to < 40 years with moderate to severe atopic dermatitis from the CHRONOS study is considered for the assessment. The results at week 52 are used. The transfer is based on the outcomes that had formed the basis for the conclusion of dossier assessment A17-63 and the decision on the procedure of dupilumab in adult patients.

Study pool and study design

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

Study CHRONOS

The known CHRONOS study is a randomized, double-blind, controlled, 3-arm parallel-group study comparing dupilumab (in 2 different dosages) + TCS with placebo + TCS in adults for 52 weeks. 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 medium-potency TCS, which could be discontinued or reinitiated as required for each individual patient. Patients with persisting or worsening symptoms received treatment escalation, referred to as “rescue therapy”, with high-potency or very high-potency TCS, systemic therapies or phototherapy. 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.

Due to the transfer of the results of the age stratum ≥ 18 to < 40 years of the CHRONOS study to children 6 months to 5 years old with severe atopic dermatitis, the risk of bias of all results considered in the present benefit assessment is considered high, analogous to the approach in A20-01 and A20-123.

Results

Morbidity

Symptoms: itching (peak pruritus numeric rating scale [NRS])

For the symptom outcome of 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. There is a hint of added benefit of dupilumab versus the comparator therapy.

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

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

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 52 versus baseline for the outcome of insomnia, measured with the Scoring Atopic Dermatitis (SCORAD) VAS on insomnia. There is a hint of added benefit of dupilumab versus the comparator therapy.

Health status (EQ-5D VAS)

For the outcome of health status, recorded using the EQ-5D VAS, no statistically significant difference between treatment groups was shown for the relevant age stratum for the mean change at week 52 compared with baseline. There is no hint of an added benefit of dupilumab in comparison with the comparator therapy; an added benefit is therefore not proven.

Health-related quality of life

Dermatology Life Quality Index (DLQI)

In the relevant age stratum, a statistically significant difference in favour of dupilumab was shown for the proportion of patients with a DLQI score of 0 or 1 at week 52. There is a hint of added benefit of dupilumab in comparison with the comparator therapy for this outcome.

Side effects

Specific adverse events (AEs)

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

In the relevant age stratum, a statistically significant difference to the disadvantage of dupilumab in comparison with the comparator therapy was shown for the outcome of eye disorders at week 52. There is a hint of greater harm from dupilumab in comparison with the comparator therapy for this outcome.

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

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

Based on the age stratum ≥ 18 to < 40 years of the CHRONOS study, the overall assessment yields positive effects in the outcome categories of morbidity and health-related quality of life for the target population of children 6 months to 5 years with severe atopic dermatitis who are candidates for systemic therapy and whose clinical picture is sufficiently similar to that of adults. These positive effects were also shown after 16 weeks in the PRESCHOOL study in patients of the target population, which was presented as supplementary information.

In the relevant age stratum, a negative effect was shown in the outcome category of side effects, caused by the outcome of eye disorders. This negative effect was not shown in the PRESCHOOL study in patients of the target population presented as supplementary information. Overall, the negative effect in the outcome of 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 of the added benefit as non-quantifiable was maintained for the relevant age stratum in the present benefit assessment.

In summary, there is a hint of a non-quantifiable added benefit of dupilumab in comparison with the ACT for children 6 months to 5 years with severe atopic dermatitis who are candidates for systemic therapy and whose clinical picture is sufficiently similar to that of adults. For children whose clinical picture is not sufficiently similar to that of adults, the added benefit is not proven.

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

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Dupilumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit[b]**
Children with severe atopic dermatitis, 6 months to 5 years old, who are candidates for systemic therapy[c]	An individually optimized treatment regimen depending on the severity of the disease and taking into account the prior therapy, under consideration of the following treatments: ▪ topical corticosteroids of classes 2 to 3 ▪ tacrolimus (topical)	▪ Children whose clinical picture is sufficiently similar to that of adults[d]: hint of a non-quantifiable added benefit ▪ Children whose clinical picture is not sufficiently similar to that of adults[d]: added benefit not proven

a. Presented is the ACT specified by the G-BA. Regarding the implementation of the ACT, the G-BA pointed out that it was assumed for the specified ACT that other, alternative drugs are used in case of intolerance, and that a placebo comparison alone does not correspond to the ACT. In addition, the G-BA pointed out that systemic corticosteroids may be indicated in the context of short-term flare therapy in children.
b. In children 6 months to 5 years, 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.
c. As per approval, the therapeutic indication comprises patients who are candidates for systemic therapy. Children 6 months to 5 years old with severe atopic dermatitis who are candidates for continuous systemic therapy are considered for the purpose of determining the ACT because the drug dupilumab is to be administered as continuous therapy and therefore represents an option only for patients who are candidates for continuous systemic therapy.
d. Regarding chronification and localization of the lesions.

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

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

I 2 Research question

The aim of the present report is to assess the added benefit of dupilumab in comparison with the ACT in children 6 months to 5 years old with severe atopic dermatitis who are candidates for systemic therapy.

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

Table 4: Research question of the benefit assessment of dupilumab

Therapeutic indication	**ACT[a]**
Children with severe atopic dermatitis, 6 months to 5 years old, who are candidates for systemic therapy[b]	An individually optimized treatment regimen depending on the severity of the disease and taking into account the prior therapy, under consideration of the following treatments: ▪ topical corticosteroids of classes 2 to 3 ▪ tacrolimus (topical)
a. Presented is the ACT specified by the G-BA. Regarding the implementation of the ACT, the G-BA pointed out that it was assumed for the specified ACT that other, alternative drugs are used in case of intolerance, and that a placebo comparison alone does not correspond to the ACT. In addition, the G-BA pointed out that systemic corticosteroids may be indicated in the context of short-term flare therapy in children. b. As per approval, the therapeutic indication comprises patients who are candidates for systemic therapy. Children 6 months to 5 years old with severe atopic dermatitis who are candidates for continuous systemic therapy are considered for the purpose of determining the ACT because the drug dupilumab is to be administered as continuous therapy and therefore represents an option only for patients who are candidates for continuous systemic therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company principally followed the G-BA's specification of the ACT, but did not mention the G-BA's notes on the ACT (see Table 4).

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. RCTs with a minimum treatment duration of 24 weeks are used for the derivation of added benefit. Such minimum treatment duration is also required as a rule by the G-BA. This deviates from the approach of the company, which considered RCTs with a minimum treatment duration of 13 weeks for the target population of children from 6 months to 5 years of age. Moreover, the company specified a minimum treatment duration of 24 weeks for patients aged ≥ 6 years. The company set this specification in order to meet the minimum treatment 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 months to 5 years as part of an evidence transfer.

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on dupilumab (status: 27 January 2023)
- bibliographical literature search on dupilumab (last search on 27 January 2023)
- search in trial registries/trial results databases for studies on dupilumab (last search on 25 January 2023)
- search on the G-BA website for dupilumab (last search on 25 January 2023)

To check the completeness of the study pool:

- search in trial registries for studies on dupilumab (last search on 25 April 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following table 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	Yes [3]	Yes [4,5]	Yes [6-10]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.
e. The age stratum ≥ 18 to < 40 years is used for the derivation of the added benefit for children from 6 months to 5 years of age.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial; TCS: topical corticosteroids

In the present data constellation, in children 6 months to 5 years, the age stratum ≥ 18 to < 40 years of the R668-AD-1224 study (hereinafter referred to as “CHRONOS” study) is used

for the benefit assessment of dupilumab in comparison with the ACT. The study is already known from the dossier assessments A17-63 [7], A19-75 [8], the corresponding addendum A20-01 [10], and dossier assessment A20-123 [9].

This deviates from the approach of the company, which included the PRESCHOOL study in children aged 6 months to 5 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 months to 5 years, as the PRESCHOOL 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 PRESCHOOL study can be used to check the transferability of the results from adults to children 6 months to 5 years of age (see below).

PRESCHOOL study unsuitable for assessing added benefit

The PRESCHOOL study used by the company is unsuitable for assessing the added benefit of dupilumab versus the ACT. The PRESCHOOL study is first described, followed by a justification of its lack of suitability for the assessment of the added benefit.

Study characteristics

Study design

The PRESCHOOL study is a 2-part phase 2/3 study of dupilumab in patients aged 6 months to 5 years. Part A is an open-label study to investigate the pharmacokinetics, efficacy and safety of dupilumab after a single-dose treatment in children with severe atopic dermatitis. Part B is a randomized, double-blind, controlled study comparing dupilumab with placebo in children with moderate to severe atopic dermatitis.

For the present assessment, only part B of the PRESCHOOL study can be used to check the transferability of the results from adults to children 6 months to 5 years of age. Part A will therefore not be considered further in the following and the further comments on the PRESCHOOL study refer exclusively to Part B.

As already described, patients aged 6 months to 5 years with moderate to severe atopic dermatitis were included. 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/or maintaining remission and low disease activity (IGA 0 to 2) despite treatment with a daily regimen of medium to higher potency TCS with or without topical calcineurin inhibitors (TCIs), applied for at least 28 days of use, or for the maximum duration recommended, whichever was shorter. Documented systemic treatment in the last 6 months prior to study inclusion was also considered as an inadequate response to topical treatments.

In the study, a total of 162 patients were randomized in a 1:1 ratio to treatment with dupilumab (N = 83) or placebo (N = 79). Randomization was stratified by weight (≥ 5 to < 15 kg versus ≥ 15 to < 30 kg), disease severity (IGA = 3 versus IGA = 4), and region (North America versus Europe versus Japan versus China). A total of 11 of the included children (6.8%) were younger than 2 years at study start.

Dosing of dupilumab was in compliance with the approval [11,12], weight-dependent, once every 4 weeks, subcutaneously: Patients ≥ 5 to < 15 kg received 200 mg dupilumab, patients ≥ 15 to < 30 kg received 300 mg dupilumab. Patients in the comparator arm received placebo subcutaneously every 4 weeks.

The treatment duration was 16 weeks. Subsequently, patients had the opportunity to participate in the open-label, single-arm R668-AD-1434 study. Patients who declined to participate in the R668-AD-1434 study were followed up for 12 weeks as part of the PRESCHOOL study.

Disease severity

The objective severity of the disease (moderate to severe atopic dermatitis) was defined in the PRESCHOOL study using the following criteria: proportion of affected body surface area ≥ 10% and Eczema Area and Severity Index (EASI) ≥ 16 and IGA ≥ 3. However, the approval of dupilumab only covers patients 6 months to 5 years old with severe atopic dermatitis.

In 2021, checklists were published for determining the indication for systemic therapy in adults, adolescents and children aged 6 to 11 years [13-15]. These include, among other things, criteria for the classification of objective severity. To date, there is no official checklist for children aged 6 months to 5 years. However, since dupilumab in children aged between 6 and 11 years is also only approved for severe atopic dermatitis, as in the target population of the present benefit assessment, the checklist is used in the present situation as an approximation for the assessment of objective severity, among other things.

According to the checklist, relevant objective severity, i.e. in the present case severe atopic dermatitis, is present if ≥ 1 of the following criteria is fulfilled:

- global severity (IGA) ≥ 4 on a 5-part scale or
- EASI > 21 or
- SCORAD > 50/objective SCORAD (oSCORAD) > 38 or
- treatment-refractory affection of > 15% body surface area or
- treatment-refractory eczema in sensitive/visible areas or
- high frequency of relapses (> 10/year) with current treatment

Based on IGA = 4, 77% of the included children had severe atopic dermatitis. For the PRESCHOOL study, data on EASI and SCORAD are available which, in deviation from the checklist, include the threshold values of 21 and 50, respectively. About 83% of the children had an EASI ≥ 21. Based on the proportion of patients with a SCORAD ≥ 50 of 98%, the criterion of relevant objective severity is fulfilled for almost all patients in Part B of the PRESCHOOL study (see Table 12 in I Appendix B of the full dossier assessment). Furthermore, no important effect modifications were shown for the different characteristics of disease severity for which subgroup analyses are available for the PRESCHOOL study (EASI < 21 versus ≥ 21, IGA = 3 versus IGA = 4, itching– worst scratch/itch NRS < 7 versus ≥ 7).

In the present situation, the total population of the PRESCHOOL study can be used to check the transferability of the results from adults to children 6 months to 5 years of age (see below).

Suitability of patients for systemic therapy

As described in the section above, checklists were published for determining the indication for systemic therapy in adults, adolescents and children aged 6 to 11 years [13-15]. For children aged 6 months to 5 years, the checklist for children aged 6 to 11 years is used as an approximation to assess suitability for systemic therapy for the patients included in the PRESCHOOL study.

According to the checklist, patients are eligible for systemic therapy if they exhibit relevant objective severity (e.g. determined using the EASI > 21, the SCORAD > 50 or body surface area involvement > 15%, see above), relevant subjective burden (based on the Children's Dermatology Life Quality Index [CDLQI] measuring health-related quality of life [CDLQI > 10], itching [> 6 on a VAS or NRS of 0 to 10], or relevant disturbance of night-time sleep due to itching/eczema), and lack of treatment response. The European guideline, in contrast, does not specify any strict subjective criteria for establishing the indication for systemic therapy [16,17].

Almost all patients had relevant objective severity of disease based on the proportion of patients with a SCORAD ≥ 50 (see Table 12 in I Appendix B of the full dossier assessment) of 98% as a criterion of relevant objective severity.

For the assessment of relevant subjective burden, a score of the CDLQI > 10, among others, is mentioned according to the above-mentioned checklist. Since the PRESCHOOL study used the Infants' Dermatitis Quality of Life Index (IDQOL) as an instrument for assessing quality of life in children < 4 years, both CDLQI and IDQOL are considered. Values between 0 and 30 are possible for both instruments [18-20], so that the threshold value of 10 is also used for the IDQOL. Mean and standard deviations of the CDLQI and IDQOL at baseline are available (see Table 12 in I Appendix B of the full dossier assessment). Assuming normal distribution of the patients' CDLQI and IDQOL scores at baseline, the Institute used the mean values and standard

deviations to estimate the proportions of children above the threshold of 10. According to this estimation, 90% of the children had a CDLQI or IDQOL > 10 and thus fulfilled the criterion of relevant subjective burden.

The lack of treatment response is already fulfilled by the inclusion criteria of the PRESCHOOL study. Patients had to have had an inadequate response to topical treatment (see above for definition) or documented systemic treatment in the last 6 months prior to study inclusion.

Overall, it is assumed that systemic therapy is an option for the study population of the PRESCHOOL study, since – assuming normal distribution for the assessment of relevant subjective burden – the criteria for systemic therapy were fulfilled with sufficient certainty in more than 80% of the patients.

Background therapy and rescue therapy

7 days before the first administration of the study medication at the latest, the patients had to use emollients as background therapy at least twice daily, whereby at least 11 of a total of 14 possible applications were sufficient for study inclusion. 14 days prior to initiation of treatment with the study medication, standardized background therapy with low-potency TCS was initiated on skin areas with active lesions. Based on physician's discretion, low-potency TCS could also be used on areas of thin skin (e.g. face, neck, genital area). With an IGA ≤ 2, the use of low-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. If lesions returned, treatment with low-potency TCS was reinstituted. With an IGA ≥ 3 or intolerable symptoms under treatment with low-potency TCS once daily, the therapy could be escalated.

Treatment escalation with medium or high-potency TCS (each once daily), TCIs (on areas of thin skin), systemic corticosteroids as well as systemic nonsteroidal immunosuppressants was called rescue therapy in the PRESCHOOL study and was only allowed after day 14. According to the study documents, these therapies were only permitted as rescue therapies, but are listed in Module 4 I of the dossier (Section 4.3.1.2.1) predominantly as concomitant medication, which is why this information is referred to below. If possible, initial escalation was to be with topical treatment with medium or high-potency TCS. Only patients who had not shown adequate improvement after at least 7 days of topical treatment 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 corticosteroids (3 of 83 children in the dupilumab arm and 6 of 78 children in the comparator arm). No child received systemic nonsteroidal immunosuppressants as treatment escalation. 33 of 83 children (40%) in the dupilumab arm and 52 of 78 children (67%) in the comparator arm received treatment escalation with medium-potency TCS. 4 children (5%) in the dupilumab arm and 15 children (19%) in the comparator arm received high-potency TCS.

Lack of implementation of the appropriate comparator therapy

The G-BA specified an individually optimized treatment regimen under consideration of TCS of classes 2 to 3 and tacrolimus (topical) as ACT. In addition, systemic corticosteroids may be indicated in the context of short-term flare therapy. However, individual decisions on which therapy would have been optimal for each patient on study entry were not planned in the PRESCHOOL study. In the PRESCHOOL study, all children received a uniform background therapy with low-potency TCS at the beginning of the study; treatment escalation to medium or high-potency TCS or tacrolimus (topical) corresponding to the ACT, without permanent treatment discontinuation, was only allowed after day 14 and only in case of intolerable symptoms. The same applied to the use of systemic corticosteroids, whereby their use led to permanent treatment discontinuation (see above).

Based on the severity classification according to EASI [21] and SCORAD [16], most patients had severe disease. According to the IGA classification of severity [22], more than 75% in both treatment arms had severe disease (IGA = 4) (see Table 12 in I Appendix B of the full dossier assessment). The average body surface area affected by atopic dermatitis was 58%. For this reason, it is assumed that using only low-potency TCS at baseline was not sufficient for the patients in the comparator arm. In addition, using only class I TCS at baseline does not correspond to the ACT.

The ACT was also not adequately implemented during the course of the study. Thus, in the comparator arm, only 8 (10.1%) children received rescue therapy at week 2, and only 16 of 79 (20.3%) children at week 3. From week 12 to week 16, the proportion of patients with rescue therapy was 62% in the comparator arm. However, only 1 child (1.3%) at week 12, and only 4 out of 79 (5.1%) children at week 16 were lesion-free (IGA = 0) or almost lesion-free (IGA = 1). In addition, it is unclear how long the rescue therapy was administered to the individual children. Using only class I TCS in a relevant proportion of children with predominantly severe symptoms over the entire course of the study is therefore not appropriate and does not correspond to the ACT.

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 are treated with topical therapies also after the skin changes have subsided (intermittent subsequent treatment; once to twice weekly) [16,23,24]. 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 used in case of intolerable symptoms, neither the reactive nor the proactive treatment approach was implemented in the comparator arm of the PRESCHOOL study. The study documents

provide no information on the extent to which the proactive treatment approach would have represented the individually optimized treatment strategy for some of the patients.

In summary, the ACT of an individually optimized treatment regimen was not implemented in the PRESCHOOL study.

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

The treatment duration of the PRESCHOOL study used by the company was 16 weeks. Thus, the PRESCHOOL study does not fulfil the minimum treatment duration of 24 weeks in the present therapeutic indication. The company referred to the comments of the Ethics Committee at the German Medical Association [25], which only advocates 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 months to 5 years. According to the company, it used additional long-term data from the RCT CHRONOS in adults for the early benefit assessment to report results over 24 weeks, which is a requirement for chronic diseases, for this patient group. In addition to the PRESCHOOL study, the company therefore used results from the CHRONOS study in adults with moderate to severe atopic dermatitis at week 52 in order to transfer these results to the target population of children aged 6 months to 5 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 6 months to 5 years old 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 PRESCHOOL study is therefore overall too short to assess long-term effects of dupilumab on the chronic-inflammatory course of atopic dermatitis. However, the PRESCHOOL study can be used to investigate the transferability of the results of the CHRONOS study to children 6 months to 5 years old (see below). The characteristics of the study, the intervention and the patients of the PRESCHOOL study are presented in Table 10, Table 11 and Table 12 in I Appendix B of the full dossier assessment.

Study CHRONOS

The CHRONOS study was already used in dossier assessments A17-63 [7], A19-75 [8] and the corresponding addendum A20-01 [10], as well as in A20-123 [9] for the assessment of added benefit of dupilumab versus the ACT in adults and adolescents with moderate to severe atopic

dermatitis, and children 6 to 11 years of age with severe atopic dermatitis who are candidates for systemic therapy. The study is a randomized, double-blind, controlled, 3-arm parallel-group study comparing dupilumab (in 2 different dosages) + TCS with placebo + TCS for 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).

Starting 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 medium-potency TCS, which could be discontinued or reinitiated as required for each individual patient. Patients with persisting or worsening symptoms received treatment escalation, referred to as "rescue therapy", with high-potency or very high-potency TCS, systemic therapies or phototherapy.

See dossier assessment A17-63 [7] 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 children aged 6 months to 5 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 from the RCT PRESCHOOL are available for children 6 months to 5 years old with severe atopic dermatitis who are candidates for systemic therapy. Children with moderate to severe atopic dermatitis were included. Nevertheless, the total population is considered, since according to the threshold values of the EASI and SCORAD instruments for assessing severity, the proportion of children with severe atopic dermatitis was above 80% with sufficient certainty (see above). However, the PRESCHOOL 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, the treatment duration was not long enough to permit conclusions on the added benefit of long-term dupilumab administration in atopic dermatitis.

In the present data constellation, the results of adults from the CHRONOS study can only be transferred to children whose clinical picture is sufficiently similar to that of adults. For children whose clinical picture is not sufficiently similar to that of adults, no conclusion on added benefit can be drawn on the basis of the available data. This is justified below.

The clinical picture of atopic dermatitis is heterogeneous overall [26-28]. In particular, the clinical picture of early childhood atopic dermatitis differs from that of adults [29]. Thus, the

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

clinical picture in the first months is characterized by acute lesions on the cheeks with itchy papules and papulovesicles, oozing plaques and crusts [29,30]. In addition, the scalp, neck, extensor muscles and trunk can also be affected. Only gradually do chronic lesions appear. About 1 to 2 years after disease onset, lichenified, chronic lesions dominate, especially flexural eczema with lichenification and dry scaling [26,29,30]. These are characteristic of the clinical picture in adults [29,31].

Since the PRESCHOOL study included children from 6 months of age, the presence of atopic dermatitis that has become chronic was not an inclusion criterion. In the PRESCHOOL study, however, only about 7% of the children were younger than 2 years at study start. In addition, disease duration was at least 3 years in 65% of the children included (see Table 12 of the full dossier assessment). It can therefore be assumed that the majority of the study population already had chronic atopic dermatitis or chronic lesions. However, there were also children with atopic dermatitis that had only been present for a short time (disease duration of 0 years), and whose disease had therefore not yet become chronic. Their proportion is unclear. The CHRONOS study, in contrast, only included adults with chronic atopic dermatitis.

The effects of differences in chronification and localization of the disease in the 2 patient populations are unclear. For this reason, in the present data constellation, a transfer is only possible to those children whose clinical picture is sufficiently similar to that of adults.

While there are molecular differences, e.g. in cytokine concentrations in the blood, compared with adults (and also with further age groups [6 to 11 years, 12 to 17 years]) [31-35], according to the current state of research, these differences are not considered sufficient to question the transferability of the results from adults to children 6 months to 5 years.

In addition, in the present data constellation, the following characteristics of the CHRONOS and PRESCHOOL studies support the transferability of the results of adults from the CHRONOS study to those children whose clinical picture is sufficiently similar to that of adults:

- In the CHRONOS study, no important effect modification by age and severity of the disease was observed.
- Overall, the PRESCHOOL study showed consistent and large effects across the different outcomes at week 16, both within the study and in comparison with the CHRONOS study at week 24 [8] and week 52, as well as in comparison with the studies AD-1526 in 12 to < 18-year-olds [8] and AD-1652 in 6 to < 12-year-olds [9] (each at week 16).

In terms of disease severity, the approved therapeutic indication of dupilumab differs between adults (moderate to severe atopic dermatitis) and children 6 months to 5 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 once again 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 severity based on EASI [21] and SCORAD [16], most patients (> 80%) in the total population and the relevant age stratum of the CHRONOS study had severe disease according to calculations conducted by the Institute based on mean values and standard deviations under assumption of a normal distribution. According to the classification of severity based on IGA [22], the proportions of moderate (IGA = 3) and severe (IGA = 4) disease were almost equal in both treatment groups. As the CHRONOS study did not show any important effect modification by disease severity (see Section I 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 months to 5 years with severe atopic dermatitis whose clinical picture is sufficiently similar to that of adults 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 are used. The transfer is based on the outcomes that had formed the basis for the conclusion of dossier assessment A17-63 [7] and the decision on the procedure of dupilumab in adult patients [36,37]. The patient characteristics of the age stratum ≥ 18 to < 40 years are presented in Table 13 in I Appendix C of the full dossier assessment; they are comparable to those of the total population particularly with regard to 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 total population, see dossier assessment A17-63 [7].

The results of the PRESCHOOL study on the outcomes from dossier assessment A17-63 used in the present benefit assessment are presented as supplementary information in I Appendix D 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 in the comparator arm received predetermined uniform treatment with medium-potency TCS and/or TCIs at the start of the study without consideration of prior therapies, despite previous inadequate response to topical (and/or systemic) therapies. An individual therapeutic strategy on study entry was thus not planned.

Within the first 2 treatment weeks, the use of a rescue therapy resulted in discontinuation of the study medication. In the relevant age stratum, the proportion of patients who discontinued treatment 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 are 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 [7].

Summary

The age stratum ≥ 18 to < 40 years with moderate to severe atopic dermatitis of the CHRONOS study is used for the assessment of the added benefit of dupilumab in comparison with the ACT in children 6 months to 5 years with severe atopic dermatitis who are candidates for systemic therapy. The results in adults from the CHRONOS are transferred only to children of the target population whose clinical picture is sufficiently similar to that of adults. For children of the target population whose clinical picture is not sufficiently similar to that of adults, no conclusion on added benefit can be drawn on the basis of the available data.

The PRESCHOOL study is unsuitable for the derivation of an added benefit in comparison with the ACT. The results of the PRESCHOOL study are presented as supplementary information in I Appendix D of the full dossier assessment.

Transferability of the study results to the German health care context

Taking into account the locations where the study was conducted, the patient characteristics (family origin and demographic parameters) and the prior and rescue therapies administered, the company considered the results of the PRESCHOOL study to be transferable to the German health care context. As described above, the PRESCHOOL study is unsuitable for answering the research question of the present benefit assessment.

The company considered 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.

I 4 Results on added benefit

I 4.1 Outcomes included

In the present data constellation, only those outcomes are used that formed the basis for the conclusion of dossier assessment A17-63 and the decision on the procedure of 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 VAS of the EQ-5D
- Health-related quality of life, measured with the DLQI
- Side effects
  - eye disorders (SOC, AEs)
  - presented as supplementary information: conjunctivitis (broad Custom Medical Dictionary for Regulatory Activities [MedDRA] Query [CMQ])

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

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 explanations of the company, the types of analysis considered adequate in dossier assessments A19-75 [8] and A20-123 [9] were used for this purpose.

In Section 4.2.5.2.1.1 of Module 4 I, the company stated that, for dichotomous efficacy outcomes, it had used the sensitivity analysis that – irrespective of the administration of a rescue therapy – was based on the actually observed values, and that it had imputed missing values using the last observation carried forward (LOCF) strategy.

For continuous outcomes, the company explained that it had used the analysis that – irrespective of the administration of a rescue therapy – was based on the actually observed values and, in addition, imputed 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). This 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 I are based on the final data cut-off of the CHRONOS study, the values of the total population presented as supplementary information deviate numerically from the results presented in A17-63 (see Section I 4.3). However, as these deviations did not result in a qualitatively different conclusion, the data on the total population reported in Module 4 I of the dossier are presented for this benefit assessment.

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

I 4.2 Risk of bias

See dossier assessment A17-63 [7] for the assessment of the risk of bias across outcomes of the CHRONOS study.

Due to the transfer of the results in the age stratum ≥ 18 to < 40 years of the CHRONOS study to children 6 months to 5 years old with severe atopic dermatitis, the risk of bias of all results considered in the present benefit assessment is considered high, analogous to the approach in A20-01 [10] and A20-123 [9].

I 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 who are candidates for systemic therapy. 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.

I Appendix E of the full dossier assessment presents the results on the outcomes of 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

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 (broad CMQ)[d]					
Stratum ≥ 18 to < 40 years				ND	
Total population (supplementary information)	*110*	*27 (24.5)*	*315*	*35 (11.1)*	*2.21 [1.40; 3.47]; < 0.001[e]*

a. In some cases, the data in the present dossier lead to numerically different values compared with A17-63 (total population) or A20-01 (stratum ≥ 18 to < 40 years), but this does not lead to a qualitatively different conclusion. Unless stated otherwise, the values reported in Module 4 I of the dossier are presented.
b. Percentage of patients with a decrease by ≥ 4 points from baseline to week 52, with a scale range of 0 to 10. Lower values indicate an improvement in symptoms.
c. Logistic regression model, adjusted for randomization stratification variables.
d. Post hoc operationalization on conjunctivitis with 16 PTs (conjunctivitis broad CMQ). The investigation of conjunctivitis events is based on the increased occurrence of conjunctivitis as well as further selected eye disorders under treatment with dupilumab. The data are from dossier assessment A17-63 [7].
e. Institute's calculation: 95% CI asymptotic; unconditional exact test, (CSZ method according to [38]).

CI: confidence interval; CMQ: Custom MedDRA Query; CSZ: convexity, symmetry z-score; DLQI: Dermatology Life Quality Index; 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 SMD: −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* *SMD: −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 SMD: −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* *SMD: −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* *SMD: 0.38 [0.15; 0.61]*

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]
a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers. b. MI analysis of the ITT population. Analysis of covariance (ANCOVA) with corresponding baseline values, treatment arm and randomization stratification variables (region and disease severity [IGA 3 vs. IGA 4] at baseline) as covariables. All observed values are included in the analysis, missing values are imputed by 2-stage MI (MCMC and regression analysis). c. In some cases, the data in the present dossier lead to numerically different values compared with A17-63 (total population) or A20-01 (stratum ≥ 18 to < 40 years), but this does not lead to a qualitatively different conclusion. The values reported in Module 4 I of the dossier are presented. d. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention (scale range of 0 to 28 [POEM] or 0 to 10 [SCORAD VAS]). e. Higher (increasing) values indicate improved health status; positive effects (intervention minus control) indicate an advantage for the intervention (scale range of 0 to 100). ANCOVA: analysis of covariance; CI: confidence interval; MCMD: Markov Chain Monte Carlo; MD: mean difference; MI: multiple imputation; 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 I 3.1, the results in 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 6 months to 5 years with severe atopic dermatitis.

On the basis of the available information, 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 of 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 ≥ 18 to < 40 years. This effect was also shown for the total population presented as supplementary information. There is a hint of added benefit of dupilumab versus the comparator therapy.

In the commenting procedure on benefit assessment A19-75, the company submitted documents to classify itching severity [39]. According to this, severe itching commences at a value of 7. Since the mean baseline value of 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) (see Table 13 in I Appendix C of the full dossier assessment), the outcome of itching (peak pruritus NRS) is assigned to the outcome category of serious/severe symptoms/late complications in the present assessment, analogous to the assessment in A20-01 [10] and A20-123 [9].

Patient-reported symptoms (POEM)

The mean change between week 52 and the start of the study was considered for patient-reported symptoms recorded using POEM. For this outcome, a statistically significant difference in favour of dupilumab was shown for the relevant age stratum≥ 18 to < 40 years and for the total population presented as supplementary information. A standardized mean difference (SMD) 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. There is a hint of added benefit of dupilumab versus the comparator therapy.

Analogous to the assessment in A17-63 [7], A19-75 [8], A20-01 [10], and A20-123 [9], the outcome of patient-reported symptoms (POEM) is assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Symptoms: insomnia (SCORAD-VAS)

For the outcome of insomnia, measured with the SCORAD VAS on insomnia, a statistically significant difference in favour of dupilumab was shown for the relevant age stratum ≥ 18 to < 40 years and for the total population presented as supplementary information for the mean change at week 52 versus baseline. An SMD 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. There is a hint of added benefit of dupilumab versus the comparator therapy.

Analogous to the assessment in A17-63 [7], A20-01 [10], and A20-123 [9], the outcome of insomnia (SCORAD VAS) is assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Health status (EQ-5D VAS)

For the outcome of health status, recorded using the EQ-5D VAS, no statistically significant difference between treatment groups was shown for the relevant age stratum ≥ 18 to < 40 years for the mean change at week 52 compared with baseline. A statistically significant difference in favour of dupilumab was shown for the total population presented as supplementary information. An SMD 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. There is no hint of an added

benefit of dupilumab in comparison with the comparator therapy; an added benefit is therefore not proven.

Health-related quality of life

DLQI

In the relevant age stratum ≥ 18 to < 40 years, a statistically significant difference in favour of dupilumab was shown for the proportion of patients with a DLQI score of 0 or 1 at week 52. This effect was also shown for the total population presented as supplementary information. There is a hint of added benefit of dupilumab in comparison with the comparator therapy for this outcome.

Side effects

Specific AEs

Eye disorders (SOC, AEs)

In the relevant age stratum ≥ 18 to < 40 years, a statistically significant difference to the disadvantage of dupilumab in comparison with the comparator therapy was shown for the outcome of eye disorders at week 52. This effect was also shown for the total population presented as supplementary information.

The present benefit assessment additionally considers the broad CMQ of conjunctivitis. This outcome comprises 16 Preferred Terms (PTs), which represent the AE of conjunctivitis more comprehensively than the SOC eye disorders. The PTs “conjunctivitis”, “conjunctivitis bacterial” and “conjunctivitis viral”, for instance, which were not included in the SOC eye disorders, are comprised in the operationalization of conjunctivitis (broad CMQ).

No data are available for the relevant age stratum ≥ 18 to < 40 years of the CHRONOS study for the outcome of conjunctivitis (broad CMQ). For the results of the total population at week 52 presented as supplementary information, a statistically significant difference to the disadvantage of dupilumab in comparison with the comparator therapy was shown for the outcome of conjunctivitis (broad CMQ).

Overall, there is a hint of greater harm from dupilumab in comparison with the comparator therapy for the outcome of eye disorders (SOC, AEs).

I 4.4 Subgroups and other effect modifiers

See dossier assessment A17-63 [7] 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 I 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 I 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 at week 52 was found for the characteristic of age for the EASI 90 outcome presented as supplementary information in I Appendix E of the full dossier assessment ($p = 0.0161$). This effect modification has an influence on the importance of the results for the total population, as it suggests an increase of the effect towards older age. Despite this interaction, there is no important effect modification by age across the considered outcomes for the CHRONOS study at week 52. The transfer of the results from the age stratum ≥ 18 to < 40 years to the target population of children whose clinical picture is sufficiently similar to that of adults is thus not called into question.

In addition, interactions for 2 outcomes were observed for the characteristic of disease severity (IGA = 3 versus IGA = 4). An interaction ($p = 0.0425$) suggesting an increase of the effect towards lesser severity of atopic dermatitis was found for the outcome of 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 ($p < 0.0001$) was also found for the EASI 75 outcome presented as supplementary information in I Appendix E of the full dossier assessment, suggesting an increase of the effect towards greater severity of atopic dermatitis. Here again, the effects were in the same direction. Despite these interactions, there was no significant effect modification by disease severity across the considered outcomes for the CHRONOS study at week 52. The transfer of the results of the CHRONOS study to children 6 months to 5 years with severe atopic dermatitis whose clinical picture is sufficiently similar to that of adults is thus not called into question.

For the best possible approximation to the target population of children 6 months to 5 years with severe atopic dermatitis whose clinical picture is sufficiently similar to that of adults, in the present data situation, the age stratum ≥ 18 to < 40 years with moderate to severe atopic dermatitis of the CHRONOS study is used in the present benefit assessment (see Section I 3.1).

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *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 taken into account in the overall conclusion on the extent of added benefit.

Table 8: Positive and negative effects from the assessment of dupilumab + TCS compared with an individually optimized treatment regimen[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: "considerable" ▪ Insomnia (SCORAD VAS): hint of an added benefit – extent: "minor"	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. In children 6 months to 5 years, 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. The results are only transferred for children whose clinical picture is sufficiently similar to that of adults.

DLQI: Dermatology Life Quality Index; NRS: numeric rating scale; POEM: Patient Oriented Eczema Measure; SCORAD: Scoring Atopic Dermatitis; TCS: topical corticosteroids; 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 of morbidity and health-related quality of life for the target population of children 6 months to 5 years with severe atopic dermatitis who are candidates for systemic therapy and whose clinical picture is sufficiently similar to that of adults. These positive effects were also shown after 16 weeks in the PRESCHOOL study in patients of the target population, which was presented as supplementary information.

In the relevant age stratum, a negative effect was shown in the outcome category of side effects, caused by the outcome of eye disorders. This negative effect was not shown in the

PRESCHOOL study in patients of the target population presented as supplementary information. Overall, the negative effect in the outcome of 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 I 3.1) resulted in a classification of the added benefit as "non-quantifiable"; this classification is maintained for the relevant age stratum in the present benefit assessment.

In summary, there is a hint of a non-quantifiable added benefit of dupilumab in comparison with the ACT for children 6 months to 5 years with severe atopic dermatitis who are candidates for systemic therapy and whose clinical picture is sufficiently similar to that of adults. For children whose clinical picture is not sufficiently similar to that of adults, the added benefit is not proven.

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 with severe atopic dermatitis, 6 months to 5 years old, who are candidates for systemic therapy[c]	An individually optimized treatment regimen depending on the severity of the disease and taking into account the prior therapy, under consideration of the following treatments: ▪ topical corticosteroids of classes 2 to 3 ▪ tacrolimus (topical)	▪ Children whose clinical picture is sufficiently similar to that of adults[d]: hint of a non-quantifiable added benefit ▪ Children whose clinical picture is not sufficiently similar to that of adults[d]: added benefit not proven
a. Presented is the ACT specified by the G-BA. Regarding the implementation of the ACT, the G-BA pointed out that it was assumed for the specified ACT that other, alternative drugs are used in case of intolerance, and that a placebo comparison alone does not correspond to the ACT. In addition, the G-BA pointed out that systemic corticosteroids may be indicated in the context of short-term flare therapy in children. b. In children 6 months to 5 years, 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. c. As per approval, the therapeutic indication comprises patients who are candidates for systemic therapy. Children 6 months to 5 years old with severe atopic dermatitis who are candidates for continuous systemic therapy are considered for the purpose of determining the ACT because the drug dupilumab is to be administered as continuous therapy and therefore represents an option only for patients who are candidates for continuous systemic therapy. d. Regarding chronification and localization of the lesions (see Section I 3.1). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company. The company derived an indication of considerable added benefit Based on the results of the PRESCHOOL study and

the total population of the CHRONOS study, which it transferred to the paediatric target population.

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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