IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Dupilumab (atopic dermatitis) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Dupilumab (atopische Dermatitis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 February 2018). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CI	confidence interval
CMQ	Customized MedRA Query
DLQI	Dermatology Life Quality Index
EQ-5D	European Quality of Life Questionnaire 5 Dimension
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
MedRA	Medical Dictionary for Regulatory Activities
Peak Pruritus NRS	Peak Pruritus Numerical Rating Scale
POEM	Patient-Oriented Eczema Measure
RCT	randomized controlled trial
SAE	serious adverse event
SCORAD	Scoring Atopic Dermatitis
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
TCS	topical glucocorticoids
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

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

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug dupilumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 1 December 2017.

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 adult patients with moderate to 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

Research question	Subindication	ACT[a]
1	Adult patients with moderate to severe atopic dermatitis who are candidates for systemic treatment	An individually optimized treatment regimen depending on the severity of the disease and taking the prior therapy into account, under consideration of the following treatments: ▪ topical class 2 to 4 glucocorticoids ▪ tacrolimus (topical) ▪ UV therapy (UVA[b]/ NB-UVB) ▪ Systemic glucocorticoids (only short-term within the framework of a relapse treatment) ▪ Ciclosporin
a: Presentation of the ACT specified by the G-BA. In addition, the G-BA provides further information on the implementation of the ACT (see text). b: UVA1 is not comprised, because it was excluded. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); UVA: ultraviolet-A light		

[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].

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

The present benefit assessment only considers the target population of patients with moderate to severe atopic dermatitis who are candidates for systemic treatment. Deviating from the company's approach, the patient population with severe atopic dermatitis who are not candidates for systemic treatment with ciclosporin will not be considered separately.

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 6 months were used for the derivation of the added benefit. Such minimum treatment duration was also recommended by the G-BA. This deviates from the company's approach, which considered RCTs with a minimum treatment duration of 12 weeks.

Results

Study pool and study characteristics

The CHRONOS study was included in the benefit assessment. The CHRONOS study is a randomized, double-blind, controlled, 3-arm parallel group study on the comparison of dupilumab (in 2 different dosages) + topical glucocorticoids (TCS) with placebo + TCS. Treatment duration was 52 weeks. Besides randomized treatment, extensive adjustments of the concomitant treatment were planned depending on the course of disease. Adult patients who had had moderate to severe atopic dermatitis for at least 3 years were included.

A total of 740 patients were assigned to treatment with dupilumab 300 mg once weekly (N = 319)[4], dupilumab 300 mg once every 2 weeks (N = 106) or placebo once weekly, subcutaneously (N = 315). To maintain blinding, patients in the study arm with biweekly dupilumab administration received subcutaneous placebo injections in the weeks without dupilumab injections.

At the start of the study, standardized background therapy with moderate-potency TCS was initiated in all patients. For areas with sensitive skin, mild-potency TCS (once daily) or topical calcineurin inhibitors (TCI) were used, which could be adjusted to the needs of the individual patients. For skin textures free or almost free of lesions, treatment was reduced from moderate-

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

potency TCS to mild-potency TCS and was then discontinued. Reoccurrence of lesions entailed the reinitiation of treatment with moderate-potency TCS. When lesions persisted or worsened under treatment with moderate-potency TCS, treatment was escalated.

Treatment escalation with high-potency or very high-potency TCS, systemic glucocorticoids, systemic non-steroidal immunosuppressants as well as phototherapy were referred to as rescue therapy in the study. Within the first 2 treatment weeks, the use of a rescue therapy resulted in a discontinuation of dupilumab or placebo for the entire further course of the study. After week 2, treatment with dupilumab or placebo was discontinued in case of systemic treatment escalation or initiation of a phototherapy. In case of systemic therapies, treatment with dupilumab or placebo could be re-initiated after a wash-out phase of ≥ 5 half-lives or 1 month following the termination of the phototherapy. Patients who discontinued treatment were encouraged to further participate in all planned study visits.

Limitations of the CHRONOS study

The CHRONOS study is limited insofar as a proactive treatment approach was not planned. Within the proactive treatment approach, the affected skin areas are treated with topic therapies also after the skin changes have subsided. In the dupilumab arm, continuous administration of dupilumab (once every 2 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 topical therapies used as concomitant treatments were discontinued in all patients of the study when they were free or almost free of lesions, and they were not reinitiated before new lesions occurred. Therefore, the patients in the comparator group of the CHRONOS study could not choose the option of a proactive treatment approach. It can be learned from the study documents that about 16% of the patients in the comparator group were free or almost free of lesions in the course of the study and treatment was thus discontinued in accordance with the requirements of the study. The study documents provide no information on the number of patients for whom the proactive treatment approach would have presented the individually optimized treatment strategy. This limitation is considered in the derivation of the added benefit of dupilumab versus the comparator therapy.

Moreover, the decision on which treatment would have been the optimal option for each patient was not made on an individual basis at the start of the study. Instead, the patients of the comparator arm initially received uniform treatment with moderate-potency topical therapies at the start of the study, despite previous inadequate response to topical (and /or systemic) therapies. This potentially inadequate treatment can influence the results at the start of the study. Therefore, the derivation of the added benefit is based on the outcomes that are recorded or analysed at the end of the study.

Moreover, treatment optimization with stronger-acting topical or systemic therapies within the first 2 treatment weeks resulted in a discontinuation of the study medication for the entire further course of the study. Due to the relatively small proportion of patients, this limitation has no consequences for the present benefit assessment.

Study duration of the CAFE study too short for the assessment of sustained effects

The study CAFE included by the company in addition to the CHRONOS study, is a randomized, double-blind 3-arm study on the comparison of dupilumab (in 2 different dosages) with placebo. Moreover, all patients received a standardized background therapy with – depending on the skin region – moderate-potency or mild-potency TCS, which could be adjusted or escalated. Only patients with severe atopic dermatitis for whom therapy with ciclosporin was unsuitable for several reasons were included. Therewith, the population of the CAFE study comprised a part of the approval population of dupilumab.

Due to the treatment duration of 16 weeks, the CAFE study is not suitable for the derivation of conclusions on the added benefit of long-term dupilumab administration in patients with chronic atopic dermatitis. The study was not used for the derivation of the added benefit in the present benefit assessment.

Risk of bias at study level and outcome level

The risk of bias at study level for the CHRONOS study was rated as low.

The risk of bias for all-cause mortality and all considered side effect outcomes at outcome level was low.

The risk of bias was rated as high for the outcomes “itching” (Peak Pruritus Numerical Rating Scale [NRS]), “insomnia” (visual analogue scale [VAS] of the “Scoring Atopic Dermatitis” [SCORAD]), patient-reported symptoms (Patient-Oriented Eczema Measure [POEM]), “health status” (European Quality of Life Questionnaire 5 Dimension [EQ-5D]-VAS) as well as for “health-related quality of life”, measured with the Dermatology Life Quality Index (DLQI). The respective risk of bias results from the violation of the intention to treat (ITT) principle caused by a relevant proportion of missing values that differs between the treatment groups.

Since valid sensitivity analyses are available for the symptom outcomes “patient-reported symptoms” (POEM) and “health status” (EQ-5D VAS) as well as for “health-related quality of life”, measured using the DLQI, the certainty of results for these outcomes is not downgraded despite of a high risk of bias.

Results

The results of the second data cut-off were used for the present benefit assessment. The data cut-off was conducted after all patients had achieved week 52.

All-cause mortality

After 52 weeks, no deaths had occurred in both relevant study arms of the CHRONOS study. This resulted in no hint of an added benefit of dupilumab in comparison with the comparator therapy, an added benefit is therefore not proven.

Morbidity – symptoms: itching (Peak Pruritus NRS)

For the symptom outcome “itching” (Peak Pruritus NRS) responder analyses are used for an improvement ≥ 4 points at week 52. There was a statistically significant difference in favour of dupilumab. This resulted in a hint of an added benefit of dupilumab in comparison with the comparator therapy.

Morbidity – symptoms: insomnia (Visual Analogue Scale of the Scoring Atopic Dermatitis (SCORAD-VAS))

For the outcome "insomnia", measured using the SCORAD-VAS on “insomnia”, a statistically significant difference in favour of dupilumab was shown for the mean change at week 52 versus the start of the study. The standardized mean difference in the form of Hedges’ g was considered to check the relevance of the result. The 95% confidence interval (CI) 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 in comparison with the comparator therapy.

Morbidity – Patient-reported symptoms (POEM)

For patient-reported symptoms recorded using the POEM, the mean change between week 52 and the start of the study was considered. There was a statistically significant and relevant difference in favour of dupilumab for this outcome. The standardized mean difference in the form of Hedges’ g was considered to check the relevance of the result. The 95% CI was completely below the irrelevance threshold of –0.2. This was interpreted to be a relevant effect. There was an indication of an added benefit of dupilumab in comparison with the comparator therapy.

Morbidity – health status

For the outcome "health status" (EQ-5D VAS), a statistically significant difference in favour of dupilumab was shown for the mean change at week 52 versus the start of the study. However, the 95% CI of the standardized mean difference (Hedges’ g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. As a result, there was no hint of an added benefit of dupilumab versus the comparator therapy for this outcome; an added benefit is therefore not proven.

Health-related quality of life – (DLQI)

Regarding the proportion of patients with a DLQI score of 0 or 1 at week 52, there is a statistically significant difference in favour of dupilumab. This results in an indication of an added benefit of dupilumab in comparison with the comparator therapy.

Side effects – serious adverse events (SAEs) as well as discontinuation due to adverse events (AEs)

There was no statistically significant difference between the treatment groups for the outcome "serious adverse events" (SAEs) after week 52. There was a statistically significant difference

for the outcome “discontinuation due to AEs”, however, the effect is assumed to be no more than marginal. Hence, there was no hint of greater or lesser harm of dupilumab in comparison with the comparator therapy for these outcomes. Greater or lesser harm is therefore not proven for these outcomes.

Side effects – specific AEs

Eye disorders (System Organ Class [SOC])

A statistically significant difference to the disadvantage of dupilumab was shown for the outcome “eye disorders” (recorded with the System Organ Class [SOC] of the standardized Medical Dictionary for Regulatory Activities [MedDRA]). The results of the additionally considered outcome “conjunctivitis” (broad Customized MedDRA Query [CMQ]) are comparable with those of the SOC “eye disorders”. Altogether, this results in an indication of greater harm of dupilumab in comparison with the comparator therapy.

Infections and infestations (SOC) as well as infections that require treatment with oral antibiotics, antiviral or fungicide drugs for more than 2 weeks

No statistically significant difference between the treatment arms was shown for the outcomes “infections and infestations” as well as “infections that require treatment with oral antibiotics, antiviral or fungicide drugs for more than 2 weeks”. Hence, there was no hint of greater or lesser harm from dupilumab in comparison with the comparator therapy for the outcomes mentioned; greater or lesser harm is therefore not proven.

General disorders and administration site conditions (SOC)

A statistically significant difference to the disadvantage of dupilumab was shown for the outcome "general disorders and administration site conditions". However, the effect is no more than marginal. Hence, there was no hint of greater or lesser harm from dupilumab in comparison with the comparator therapy for the outcome mentioned; greater or lesser harm is therefore not proven.

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

In the overall consideration, there are positive effects of dupilumab in the outcome categories "morbidity" and "health-related quality of life" and a negative effect in the outcome category "side effects".

The positive effects with the extents “considerable” and “major” are contrasted with a negative effect with the extent “considerable”. This negative effect did not challenge the positive effects of dupilumab.

Due to the limitations regarding the implementation of the appropriate comparator therapy, it was unclear how far the observed extent of the effects would have been reached for the individual outcomes in the comparator group after complete implementation of an individually

optimized therapy. At the same time, complete elimination of the present effects is not assumed, due to the proportion of patients whose treatment was potentially not individually optimized (about 16%). In summary, the extent of the added benefit was therefore rated as "non-quantifiable". This results in an indication of non-quantifiable added benefit of dupilumab in comparison with the ACT for patients with moderate to severe atopic dermatitis who are candidates for systemic treatment.

The result of the assessment of the added benefit of dupilumab in comparison with the ACT is summarized in Table 3.

Table 3: Dupilumab – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with moderate to severe atopic dermatitis who are candidates for systemic treatment	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 glucocorticoids of the classes 2 to 4 ▪ tacrolimus (topical) ▪ UV therapy (UVA[b] / NB-UVB) ▪ systemic glucocorticoids (only short-term within the framework of a relapse treatment) ▪ ciclosporin	Indication of a non-quantifiable added benefit
a: Presentation of the ACT specified by the G-BA. For the implementation of the ACT, the G-BA emphasized the assumption that other, alternative drugs would be used in case of intolerances; that neither the exclusion of topical and/or systemic therapies for the treatment of the atopic dermatitis nor unchanged continuation of inadequate (pre)treatment were adequate implementations of the appropriate comparator therapy. 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 should not be considered an individually optimized treatment regimen within the framework of the envisaged therapeutic indication. Besides treatment of the relapses, adjustment of the treatment should also be possible during the chronic phases within the framework of the study. b: UVA1 is not comprised, because it was excluded. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); UVA: ultraviolet-A light		

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

2.2 Research question

The aim of the present report was to assess the added benefit of dupilumab in comparison with the ACT in adult patients with moderate to 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 on the benefit assessment of dupilumab

Research question	Subindication	ACT[a]
1	Adult patients with moderate to severe atopic dermatitis who are candidates for systemic treatment	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 glucocorticoids of the classes 2 to 4 ▪ tacrolimus (topical) ▪ UV therapy (UVA[b] / NB-UVB) ▪ systemic glucocorticoids (only short-term within the framework of a relapse treatment) ▪ ciclosporin
a: Presentation of the ACT specified by the G-BA. In addition, the G-BA provides further information on the implementation of the ACT (see text). b: UVA1 is not comprised, because it was excluded. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); UVA: ultraviolet-A light		

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

The company principally followed the G-BA's specification of the ACT, however, without indicating the comments of the G-BA on the ACT in module 3 A (see Section 2.7.1 of the full dossier assessment).

The present benefit assessment only considers the target population of patients with moderate to severe atopic dermatitis who are candidates for systemic treatment. Deviating from the company’s approach, the patient population with severe atopic dermatitis who are not candidates for systemic treatment with ciclosporin will not be considered separately.

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 6 months were used for the derivation of the added benefit. Such minimum treatment duration was also recommended by the G-BA. This deviates from the company's approach, which considered RCTs with a minimum treatment duration of 12 weeks.

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: 4 September 2017)
- bibliographical literature search on dupilumab (last search on 5 September 2017)
- search in trial registries for studies on dupilumab (last search on 4 September 2017)

To check the completeness of the study pool:

- search in trial registries for studies on dupilumab (last search on 6 December 2017)

The check identified no additional relevant study.

2.3.1 Studies included

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

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

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
R668-AD-1224 (CHRONOS[b])	Yes	Yes	No
a: Study sponsored by the company. b: In the following tables, the study is referred to with this abbreviated form. RCT: randomized controlled trial; TCS: topical glucocorticoids; vs.: versus			

In addition to the CHRONOS study included in the present benefit assessment, the company considered another RCT in its assessment (R668-AD-1424; hereinafter referred to as CAFE). This study included adults with severe atopic dermatitis for whom systemic treatment with ciclosporin was not indicated. Thus, the study population of the CAFE study represented a subpopulation of the approval population of dupilumab. However, due to the short treatment duration (16 weeks), the CAFE study considered by the company is unsuitable to assess the added benefit of dupilumab in comparison with the ACT.

CAFE study – study duration too short for the assessment of sustained effects

The CAFE study [3-8] is a randomized, double-blind, controlled 3-arm study on the comparison of dupilumab (in 2 different dosages) with placebo. Only patients with severe atopic dermatitis for whom therapy with ciclosporin was unsuitable for several reasons were included. Therewith, the population of the CAFE study comprised a proportion of the approval population of dupilumab.

A total of 325 patients of the study were randomly assigned (1:1:1) to treatment with dupilumab 300 mg once weekly, subcutaneously (N = 110), dupilumab 300 mg once every 2 weeks, subcutaneously (N = 107) or placebo (N = 108). Moreover, all patients received a standardized background therapy with moderate-potency or mild-potency TCS, depending on the skin region. Within the treatment duration, the therapy could be adjusted or escalated using stronger-acting topical or systemic therapies ("rescue therapy").

The CAFE study comprised a screening and a standardization phase of 2 weeks each as well as a 16-week randomized treatment phase. From week 16, suitable patients could participate in an open, single-arm extension phase of the CAFE study. The patients who did not participate in the extension phase, underwent follow-up treatment for further 12 weeks, starting from week 16 (follow-up phase). During the follow-up phase the patients were further treated with TCS at the physician's discretion in case of intolerable symptoms.

Due to its treatment duration of 16 weeks, the CAFE study is not suitable for the derivation of conclusions on the added benefit of long-term dupilumab administration in patients with atopic dermatitis. Atopic dermatitis is a chronic disease with a fluctuating course and flare-ups of different duration and severity [9]. Therefore, the therapy does not only focus on the treatment of acute exacerbations (relapses) in the present therapeutic indication, but also on a long-term control of the disease as well as on the prevention of relapses and the avoidance of side effects of administered therapies [9,10]. The chronicity of the disease and the individual heterogenous episodical progress with regard to duration and severity of the relapses and the lesion-free periods require a treatment duration beyond 16 weeks to capture the long-term treatment goals. Therefore, the present benefit assessment exclusively includes studies with a minimum treatment duration of 6 months. Such minimum treatment duration was also recommended by the G-BA (see Section 2.2).

CHRONOS study – subpopulation with high unmet medical need (CAFE-like)

Besides the analyses on the total population of the CHRONOS study, the company presented analyses on a subpopulation it described as patients with high unmet medical need. The company defined them as patient population with severe atopic dermatitis for whom systemic treatment with ciclosporin is unsuitable. Thus, the subpopulation of the CHRONOS study corresponded to the study population of the CAFE study, which is why the company also refers to the subpopulation as "CAFE-like". Analyses on this patient population were prespecified in the study protocol of the CHRONOS study in terms of subgroup analyses for the characteristic "high unmet medical need".

Contrary to the company's approach, only results of the total population of the CHRONOS study were considered. The patient population defined by the company is comprised in the target population for dupilumab. A separate ACT was not available for this subpopulation. Moreover, proof of an effect modification by the characteristic "high unmet medical need" was not shown in any of the subgroup analyses presented by the company.

Summary

The total population of the CHRONOS study was used for the assessment of the added benefit of dupilumab in comparison with the ACT in adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy. The 16-week treatment duration of the CAFE study is insufficient for the assessment of an added benefit of dupilumab in the present therapeutic indication of a chronic disease.

Section 2.6 of the full dossier assessment contains a reference list for the included CHRONOS study.

2.3.2 Study characteristics

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CHRONOS	RCT, double-blind, parallel	Adults with chronic moderate to severe AD and documented inadequate response to topical AD treatment[b] within the last 6 months before study inclusion; IGA ≥ 3; lesions ≥ 10% of the body surface; EASI Score ≥ 16; Peak Pruritus NRS ≥ 3	dupilumab Q2W + TCS (N = 106) dupilumab QW + TCS (N = 319)[c] placebo + TCS (N = 315)	Screening: up to 35 days Treatment duration: 52 weeks Observation: outcome-specific, follow-up: 12 weeks[d]	162 study centres in Australia, North America, Europe and Asia 10/2014–10/2016[e] First data cut-off: 27 April 2016[f] Second data cut-off: 16 December 2016[g]	Primary: EASI 75[h], IGA Secondary: morbidity, health-related quality of life, side effects

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for this benefit assessment.
b: Inadequate response to topical AD treatment is defined as not reaching or maintaining remission or low disease activity (IGA 0–2) despite treatment with moderate-potency or high-potency TCS (class II-IV) with or without TCI for at least 28 days or the maximally permitted treatment duration according to the approval. Patients with documented systemic AD treatment in the last 6 month prior to study inclusion were also rated as non-responders to topical AD treatment.
c: The arm is not relevant for the assessment and is not shown in the following tables.
d: Patients can receive further treatment with dupilumab after completion of the follow-up phase in the open-label extension study.
e: Date of the last study visit of the last patients included: 19 October 2016.
f: The first data cut-off was planned to take place after all randomized patients had reached week 16; it also included analyses on all patients who had already received week 52 at this point in time.
g: It was implemented after all patients had achieved week 52.
h: For the EU, the EU reference markets as well as Japan, IGA and EASI 75 were used as co-primary outcomes; IGA was the sole primary outcome for all other countries.

AD: atopic dermatitis; EASI: Eczema Area and Severity Index; EU: European Union; IGA: Investigator's Global Assessment; N: number of randomized patients; NRS: Numerical Rating Scale; Q2W: once every 2 weeks; QW: once weekly; RCT: randomized controlled trial; TCI: topical calcineurin inhibitors; TCS: topical glucocorticoids; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: dupilumab + TCS vs. placebo + TCS

Study	Intervention	Comparison
CHRONOS	Dupilumab 600 mg SC on day 1, then every two weeks 300 mg dupilumab SC[a]	Placebo SC once weekly
	Background therapy: ▪ ≥ 7 days before randomization and during the entire study duration: application of emollients ≥ twice daily ▪ As of day 1: ▫ use of moderate-potency TCS once daily for areas with active lesions; use of mild-potency TCS once daily (or possibly use of TCI[b]) for areas with thin skin (e.g. face, neck, genital areas) or areas for which permanent treatment with moderate-potency TCS is considered to be unsafe. For areas that are treated with TCS, emollients should only be used once daily (e.g. TCS in the morning and emollients in the evening) ▫ for controlled lesions (lesion-free or almost lesion-free skin textures) switch from moderate-potency TCS to mild-potency TCS once daily for 7 days, followed by the discontinuation of TCS ▫ recurrence of lesions requires retreatment with moderate-potency TCS ▫ lesions persisting or deteriorating under treatment with moderate-potency TCS can be treated with high-potency or very high-potency TCS once daily, systemic glucocorticoids, systemic non-steroidal immunosuppressants or phototherapy (rescue therapy)[c] ▪ reduction or discontinuation of TCS treatment might be considered if there are signs of a local or systemic TCS toxicity **Non-permitted premedication/pretreatment:** ▪ within 7 days before start of the treatment ▫ TCS/TCI ▫ all other AD drugs that might impair the efficiency or influence the assessment of the AD severity[d] ▪ within 2 weeks before start of the treatment: systemic antibiotics, virostatic drugs, parasiticides, anti-protozoals or antimycotics; in case of superficial skin infections within one week before start of the treatment[e] ▪ within 4 weeks before start of the treatment: ▫ immunosuppressants / immunomodulatory drugs (e.g. systemic steroids, ciclosporin, mycophenolate mofetil, janus kinase inhibitors, interferon-γ, azathioprine, methotrexate) ▫ phototherapy for AD ▫ regular visit to the solarium (≥ twice weekly) ▪ Biologics[e] ▪ within 12 weeks before start of the treatment: live vaccines	
	Concimitant medication/concomitant treatment: **Allowed:** ▪ Basic skin care (for skin cleaning and bathing), emollients, bleach baths, topical anaesthetics, antihistamines **Not allowed:** ▪ Start of AD treatment with prescription emollients or emollients with additives during the screening phase ▪ moist compresses, solarium ▪ immunomodulatory biologics ▪ live vaccines ▪ major elective surgeries	

(continued)

Table 7: Characteristics of the intervention – RCT, direct comparison: dupilumab + TCS vs. placebo + TCS (continued)

a: To maintain blinding, patients received placebo SC during the weeks without administration of dupilumab doses.
b: TCS and TCI should not be used in combination for treatment of the same skin areas.
c: When a rescue therapy is administered within the first 2 weeks, study treatment should be permanently discontinued. Treatment with dupilumab must be discontinued when systemic AD therapies are administered after the first 2 weeks. Treatment with dupilumab could be re-initiated after a wash-out phase of ≥ 5 half-lives or 1 month following the termination of the phototherapy.
d: Coal tar preparations, other colouring topical products, products from traditional Chinese medicine or all other AD treatments which were not used in clinical studies. Treatments of these sorts had to be discontinued ≥ 7 days before start of the treatment.
e: All substances causing cell depletion, including (but not limited to) rituximab, within 6 months before the baseline visit or until a normal lymphocyte count is achieved, depending on which period is longer; other biologics within 5 half-lives (if known) or 16 weeks before the baseline visit, depending on which period is longer.
AD: atopic dermatitis; RCT: randomized controlled trial; SC: subcutaneous; TCI: topical calcineurin inhibitors; TCS: topical glucocorticoids; vs.: versus

Study design

Study design, patient population and interventions

The CHRONOS study is a randomized, double-blind, controlled, 3-arm parallel-group study on the comparison of dupilumab (in 2 different dosages) + TCS with placebo + TCS. Treatment duration was 52 weeks. Adult patients who had had moderate to severe atopic dermatitis for at least 3 years were included.

Moreover, the patients had to have responded inadequately to other topical treatments within 6 months before study inclusion. Inadequate response to topical treatment was defined as not reaching or maintaining remission or lower disease activity (Investigator's Global Assessment [IGA 0-2]) despite treatment with moderate-potency to high-potency TCS with or without topical calcineurin inhibitors (TCI) for at least 28 days or the maximally permitted treatment duration according to the approval. Patients who had received documented systemic treatment in the last 6 months before the start of the study were also rated as non-responders to topical treatment.

The severity of the disease was defined using the following criteria: proportion of the affected body surface (Body Surface Area [BSA]) ≥ 10, Eczema Area and Severity Index (EASI) ≥ 16 and IGA ≥ 3. For the present benefit assessment, this definition of the severity grade was rated as adequate representation of moderate to severe atopic dermatitis (see Section 2.7.2.1 of the full dossier assessment).

A total of 740 patients were assigned to treatment with dupilumab 300 mg once weekly[5] (N = 319), dupilumab 300 mg once every 2 weeks (N = 106) or placebo once weekly, subcutaneously (N = 315), stratified by disease severity and region in a ratio of 3:1:3. On day 1, patients in the dupilumab arms received starting doses of 600 mg (subcutaneously) in compliance with the approval [11]. To maintain blinding, patients in the study arm with biweekly dupilumab administration received subcutaneous placebo injections in the weeks without dupilumab injections.

For the EU, the EU reference markets as well as Japan, IGA 0 to 1 including a reduction of ≥ 2 points compared with the start of the study, and EASI 75 were used as co-primary outcomes, each at week 16; IGA 0-1 at week 16 was the sole primary outcome for all other countries. Secondary relevant outcomes were symptoms, health-related quality of life, and AEs.

Background therapy and rescue therapy

At the start of the study, standardized background therapy was initiated in all patients, which could be adjusted to the needs of each individual patient in the course of the study. 7 days before the first administration of the study medication at the latest, patients had to use emollients at least twice daily, further therapies were not allowed. As of day 1, patients were treated with moderate-potency TCS once daily. For areas with thin skin (e.g. face, neck, genital areas) or areas for which permanent treatment with moderate-potency TCS was considered to be unsafe, mild-potency TCS were used once daily. or the patients received TCI. Treatment of controlled lesions (lesion-free or almost lesion-free skin textures, [corresponding to an IGA 0 to 1]) was reduced from moderate-potency TCS to mild-potency TCS once daily for a period of 7 days and was then discontinued. Reoccurrence of lesions entailed the reinitiation of treatment with moderate-potency TCS. When lesions persisted or worsened under treatment with moderate-potency TCS, treatment was escalated.

Treatment escalation with high-potency or very high-potency TCS (once daily each), systemic glucocorticoids, systemic non-steroidal immunosuppressants as well as phototherapy were referred to as rescue therapy in the study. Within the first 2 treatment weeks, the use of a rescue therapy resulted in a discontinuation of the study medication for the entire further course of the study. After week 2, treatment with dupilumab or placebo was discontinued in case of systemic treatment escalation or initiation of a phototherapy. In case of systemic therapies, treatment with dupilumab or placebo could be re-initiated after a wash-out phase of ≥ 5 half-lives or 1 month following the termination of the phototherapy. Patients who discontinued treatment were encouraged to further participate in all planned study visits.

Follow-up

The planned duration of follow-up observation of the patients comprised 12 weeks after the last study medication for the individual outcomes. Moreover, the patients had the opportunity to

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

participate in an open extension study with dupilumab at the end of the follow-up period. Patients with relapses within the follow-up observation period could enter the open extension phase also before the follow-up observation had expired. Patients who had discontinued their therapy before the planned termination of treatment could be included in the open extension study at week 56, provided that they had participated in all planned study visits before.

Limitations of the CHRONOS study

Missing option of a proactive treatment approach

For the treatment of atopic dermatitis, the guidelines recommend a proactive therapy approach besides the reactive one. Within the proactive treatment approach, the affected skin areas are treated with topic therapies also after the skin changes have subsided (intermittent subsequent treatment; once to twice weekly) [9,12-14]. This is particularly recommended for patients with lesions that frequently reoccur at the same sites [12,14,15]. Within the reactive treatment approach, topical therapies are discontinued after the acute lesions have subsided, they are only resumed after the reoccurrence of lesions.

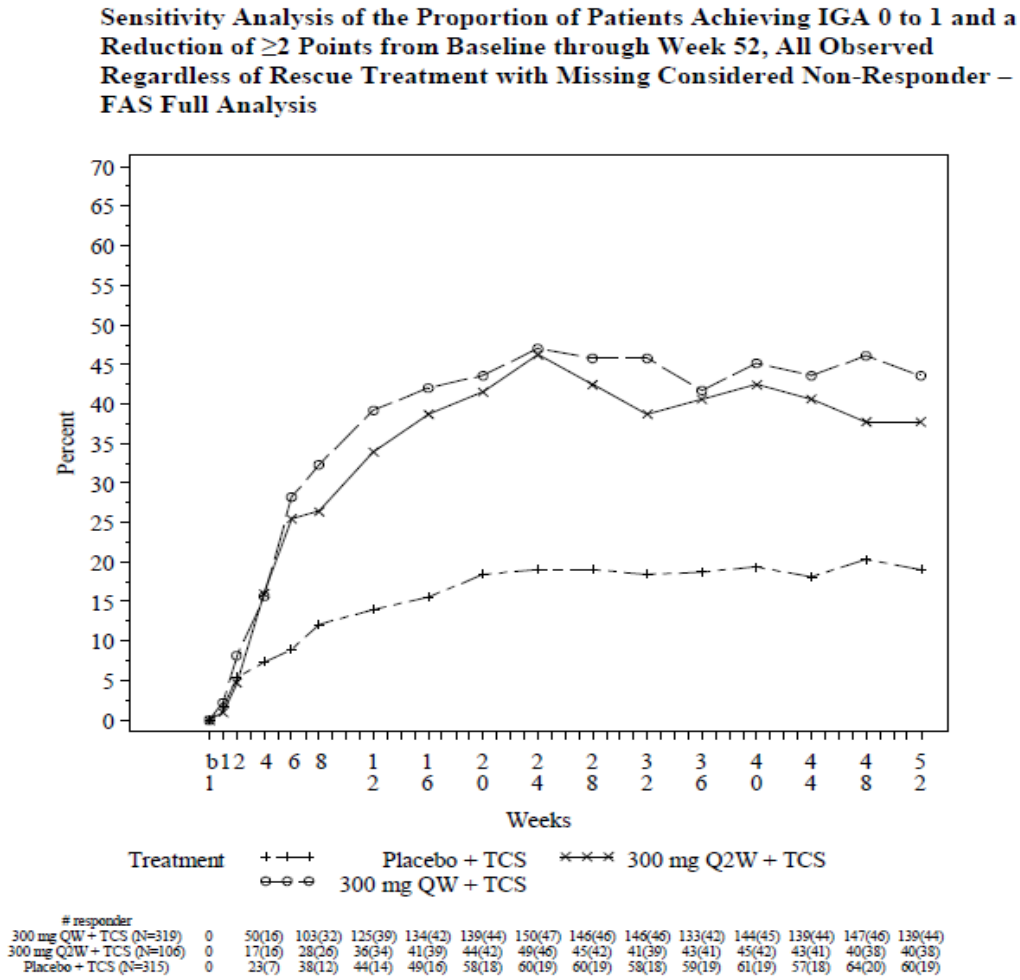
In the CHRONOS study, patients in the dupilumab arm received continuous dupilumab administration (once every two weeks) even in case of lesion-free or almost lesion-free skin textures. This is assessed as therapy strategy comparable to the proactive treatment approach in this study arm.

However, according to the study protocol the topical therapies used as concomitant treatments were discontinued in all patients of the study when they were free or almost free of lesions, and the treatments were not reinitiated before new lesions occurred. This corresponds to a reactive treatment approach. Therefore, the patients in the comparator group of the CHRONOS study could not choose the option of a proactive treatment approach. 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 severity and under consideration of the previous treatment were not completely exhausted in the comparator arm. The study documents provide no information on the number of patients for whom the proactive treatment approach would have presented the individually optimized treatment approach.

It can be learned from the Kaplan-Meier curve (Figure 1) that about 16% of the patients in the comparator group were free or almost free of lesions (IGA 0 or 1) in the course of the study from week 20 to week 52, and the treatment was thus discontinued in accordance with the requirements of the study. The study documents do not provide information on the proportion of patients with an IGA 0 (completely free of lesions).

Moreover, it can be inferred from the study documents that the average number of days on which patients in the comparator arm did not receive background therapy amounted to about 41 days within a 52-week period. Thus, the question arises as to whether and how much of the roughly 16% patients in the comparator arm who received no therapy over a significant period of time were candidates for individual proactive treatment

This limitation is considered in the derivation of the added benefit of dupilumab versus the comparator therapy.



Note: the following study arms are relevant for the present benefit assessment: 300 mg Q2W + TCS (dupilumab 300 mg every two weeks, subcutaneously) as well as placebo + TCS

Figure 1: Kaplan-Meier curve on the proportion of patients with IGA 0 to 1 as well as a reduction of ≥ 2 points from the start of the study to week 52

Restrictedly individually optimized treatment at the start of the study

In accordance with the approval, dupilumab is indicated in patients who are candidates for systemic treatment. From the company's point of view, these are patients whose disease cannot be adequately controlled with the use of topical therapies (TCS, TCI) or UV therapies, or for whom the use of topical therapies with potencies capable of causing a sufficient clinical effect is not or no longer reasonable.

If the company's criteria are taken as a basis, the relevance of the CHRONOS study is challenged. Thus, patients who had not responded to topical (and/or systemic) treatment within the last 6 months were included in the study. According to the company's definition, the use of topical therapies is not or no longer reasonable for these patients; the use of systemic therapies

must therefore be considered. At the time point of the start of the study, systemic treatment with dupilumab had been used in the intervention arm of the CHRONOS study, but not in the comparator arm. The concomitant therapies used in the course of the CHRONOS study and listed in Table 8 show that therapy escalation of the patients in the comparator arm was implemented with high-potency and very high-potency TCS and that relatively few patients received systemic treatment. The present benefit assessment does not follow the company's criteria on the suitability of the patients for systemic treatment, particularly as the ACT specified by the G-BA also includes topical therapies.

Moreover, at the start of the study, all patients of the comparator arm initially received predetermined uniform treatment with moderate-potency topical therapies without consideration of the prior therapy - despite previous inadequate response to topical (and/or systemic) therapies. 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 very high-potency topical or systemic therapies would have been the individually optimized treatment at the start of the study. It can be inferred from the study documents that 26 of 315 (8.3%) patients in the comparator arm received a rescue therapy in the first 2 weeks. This rescue therapy was defined as the use of high-potency or very high-potency TCS, systemic glucocorticoids, systemic non-steoridal immunosuppressants or phototherapy. This proportion is relatively minor, however, it cannot be ruled out that the uniform administration of moderate topical therapies at the start of the study had an impact on the study results. This becomes particularly clear as symptomatic relapses occurred more frequently in the first study weeks and decreased in the course of time (see Section 2.7.2.4.3 of the full dossier assessment).

The described limitation of the CHRONOS study did not result in the exclusion of the study from the present benefit assessment. However, the derivation of the added benefit was based on the outcomes that were recorded or analysed at the end of the study. At this point in time, the individually optimized treatment was achieved– with the exception of the proactive therapy that was not provided for in the comparator arm of the study. The results were presumably not influenced by the potentially inadequate treatment at the start of the study (see Figure 1). However, the individual results of the study are examined with regard to their usability for conclusions on the added benefit.

Table 8: Concomitant therapy – RCT, direct comparison: dupilumab + TCS vs. placebo + TCS

Study Characteristics Category	**Dupilumab + TCS**	**placebo + TCS**
CHRONOS[b]	N[a] = 110	N[a] = 315
Topical concomitant treatment, n (%)		
mild-potency TCS (class I)	54 (49.1)	147 (46.7)
moderate-potency TCS (class II)	87 (79.1)	258 (81.9)
high-potency TCS (class III)	51 (46.4)	229 (72.7)
very high-potency TCS (class III)	7 (6.4)	69 (21.9)
TCI	13 (11.8)	34 (10.8)
tacrolimus	12 (10.9)	26 (8.3)
tacrolimus monohydrate	1 (0.9)	6 (1.9)
pimecrolimus	1 (0.9)	4 (1.3)
Systemic concomitant treatment, n (%)		
glucocorticoids	16 (14.5)	53 (16.8)
calcineurin inhibitors	1 (0.9)	17 (5.4)
ciclosporin	1 (0.9)	17 (5.4)
tacrolimus monohydrate[c]	0 (0.0)	1 (0.3)
other immunosuppressants	1 (0.9)	7 (2.2)
methotrexate[c]	0 (0.0)	4 (1.3)
azathioprine[c]	1 (0.9)	3 (1.0)
selective immunosuppressants	1 (0.9)	7 (2.2)
medical procedures, n (%)		
UV light therapy	1 (0.9)	3 (1.0)
Phototherapy	1 (0.9)	0 (0.0)

a: Number of patients who were included in the safety population.
b: Information refers to the study documents at the second data cut-off (16 December 2016).
c: not approved in Germany for the treatment of atopic dermatitis.
n: number of patients with event; N: number of patients who were included in the safety population; RCT: randomized controlled trial; TCI: topical calcineurin inhibitors; TCS: topical glucocorticoids; UV: ultraviolet; vs.: versus

Discontinuation of the study medication when a rescue therapy was used at the start of the study

Within the first 2 treatment weeks, the use of a rescue therapy resulted in a discontinuation of the study medication for the entire further course of the study. It must be assumed that the background therapy was still continued for the patients - this is not clear from the study documents. It these cases, the comparator therapy was thus not compared with dupilumab, but with background therapies. The patients were required to keep the examination appointments scheduled for the course of the study, they were assessed as non-responders in the analyses. In total, 2 of 106 (1.9%) patients in the dupilumab arm and 26 of 315 (8.3%) patients in the

comparator arm received rescue therapy within the first 2 weeks. Due to the relatively small proportion of patients, this limitation has no consequences for the present benefit assessment.

Data cut-offs

Analyses on 2 data cut-offs were available for the CHRONOS study:

- The first data cut-off (27 April 2016): analysis after all randomized patients had reached week 16; it also included analyses on all patients who had already received week 52 at this point in time.
- Second data cut-off (16 December 2016): final data cut-off; conducted after all randomized patients had achieved week 52

The company based its conclusions on the added benefit on the first data cut-off. About 84% of the randomized patients who had been observed for 52 weeks were included in the analyses on the benefit outcomes. All randomized patients were included in the analysis of the harm outcomes. However, 16% of them had been observed for a shorter period.

The company justified its scheduling of the first data cut-off by referring to the European Medicines Agency (EMA), which in its description of the CHRONOS study also related to the initial analysis and explained this preference by the missing control for multiplicity for the analysis subsequently submitted [16]. The company also pointed out that, in comparison with the initial analysis, the analysis that was subsequently submitted was only supplemented with the data of the patients from the lately initiated Asian centres. Therefore, the initial analysis was more relevant for the European health care context. The company therefore presented the results of the analysis subsequently submitted (second data cut-off, including the missing patients from the Asian centres) as sensitivity analysis.

Contrary to the company's approach, the second data cut-off was used for the derivation of the added benefit in the present benefit assessment. The data cut-off was conducted after all patients had achieved week 52; it thus comprised more comprehensive information on long-term data. Considerations of the EMA on the multiplicity within the framework of the approval procedure were of subordinated importance for the downstream benefit assessment. It is correct that only further Asian patients were included in the analyses on the second data cut-off. However, this argument is not appropriate, since the analyses on the first data cut-off also included Asian patients. Based on the data presented by the company at the second data cut-off, institute's subgroup analyses were performed for the characteristic "region" to check for a potential effect modification. These showed no relevant effect modification for the patient-relevant outcomes of the CHRONOS study.

Types of analysis

The primary analysis of the CHRONOS study comprised a non-responder imputation in case of binary variables and, in case of continuous variables, a multiple imputation (MI) method with censoring for patients after administration of a rescue treatment or in case of missing

values. According to the company's assessment, this kind of imputation is considered unsuitable for the investigation of an added benefit of dupilumab in comparison with an individually optimized treatment regimen, since treatment escalation (e.g. rescue treatment) must be considered a part of the individual adjustment of therapy (optimization).

A series of sensitivity analyses were prespecified in the CHRONOS study. As analysis relevant for the benefit assessment, the company used the sensitivity analysis which was based on the actually observed values without imputation of missing values, independent of the implementation of a rescue therapy. Deviating from the company, an analysis strategy which used the observed values after a rescue therapy, but in which missing values were adequately imputed, was chosen as adequate analysis for the present benefit assessment.

For continuous outcomes, this corresponds to a sensitivity analysis prespecified (but not used by the company) within the framework of the CHRONOS study. The study documents include no such analysis for dichotomous outcomes. Therefore, institute's analyses were conducted on the basis of the analysis used by the company, in which missing values were imputed in both treatment arms according to the proportion of events in the control group. For the dichotomous outcomes, the present benefit assessment presents both the results of the analysis considered by the company and the institute's calculation, whereby the derivation of the added benefit is based on the latter analysis (see Section 2.7.2.2 of the full dossier assessment).

Characteristics of the study population

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: dupilumab + TCS vs. placebo + TCS

Study Characteristics Category	**dupilumab + TCS**	**Placebo + TCS**
CHRONOS	N[a] = 106	N[a] = 315
Age [years], mean (SD)	40 (14)	37 (13)
Ethnicity, n (%)		
White	74 (69.8)	208 (66.0)
Black or African American	2 (1.9)	19 (6.0)
Asian	29 (27.4)	83 (26.3)
Other	1 (0.9)	5 (1.6)
Sex [F/M], %	42/58	39/61
Region, n (%)		
North and South America	36 (34.0)	108 (34.3)
Asia-Pacific	27 (25.5)	81 (25.7)
Eastern Europe	29 (27.4)	83 (26.3)
Western Europe	14 (13.2)	43 (13.7)
Duration of disease [years], mean (SD)	30.1 (15.5)	27.5 (14.3)
EASI, mean (SD)	33.6 (13.3)	32.6 (12.9)
IGA, n (%)		
IGA = 3	53 (50.0)	168 (53.3)
IGA = 4	53 (50.0)	147 (46.7)
Peak Pruritus NRS, mean (SD)	7.4 (1.7)	7.3 (1.8)
NRS ≥ 3, n (%)	105 (99.1)	306 (97.1)
NRS ≥ 4, n (%)	102 (96.2)	299 (94.9)
Affected body surface (%), mean (SD)	59.5 (20.8)	56.9 (21.7)
SCORAD, mean (SD)	69.3 (15.2)	66.0 (13.5)
POEM, mean (SD)	20.3 (5.7)	20.0 (6.0)
Treatment discontinuation, n (%)	13 (12.3)	90 (28.6)
Study discontinuation, n (%)	9 (8.5)	59 (18.7)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.

EASI: Eczema Area and Severity Index; F: female; IGA: Investigator's Global Assessment; m: male; n: number of patients in the category; N: number of randomized patients; NRS: Numerical Rating Scale; POEM: Patient-Oriented Eczema Measure; RCT: randomized controlled trial; SCORAD: Scoring Atopic Dermatitis; SD: standard deviation; TCS: topical glucocorticoids; vs.: versus

Patient characteristics were sufficiently balanced between the 2 relevant treatment arms.

The mean age of the patients in the relevant study arms was about 40 years; most of them were male and white. The mean disease duration of the atopic dermatitis was about 30 years.

According to the classification of the severity grades based on EASI [17] or SCORAD [12], most of the included patients had severe forms of illness. According to the classification of the severity grades based on IGA, moderate and severe forms of disease were equally represented in both treatment groups. On average, about 60% of the body surface were affected by atopic dermatitis.

The proportion of treatment discontinuations in the comparator arm amounted to about 29% and was thus more than twice as high compared with the roughly 12% in the dupilumab arm. The same also applies to the proportion of study discontinuations (8.5% vs. 18.7%).

Table 10 shows the prior therapies of the patients in the CHRONOS study.

Table 10: Characteristics of the study population (prior therapy) – RCT, direct comparison: dupilumab + TCS vs. placebo + TCS

Study **Characteristics** **Category**	**Dupilumab + TCS**	**Placebo + TCS**
CHRONOS	N[a] = 110	N[a] = 315
Prior topical treatment[b], n (%)		
mild-potency TCS (class I)	21 (19.1)	59 (18.7)
moderate-potency TCS (class II)	46 (41.8)	131 (41.6)
high-potency TCS (class III)	74 (67.3)	218 (69.2)
very high-potency TCS (class III)	28 (25.5)	79 (25.1)
TCI[c]	36 (32.7)	101 (32.1)
Prior systemic therapy[d] n (%)		
glucocorticoids	42 (38.2)	116 (36.8)
calcineurin inhibitors[e]	34 (30.9)	89 (28.3)
other immunosuppressants[f]	15 (13.6)	47 (14.9)
selective immunosuppressants[g]	12 (10.9)	18 (5.7)
interleukin inhibitors	0 (0.0)	2 (0.6)
Medical procedures, n (%)		
UV light therapy	7 (6.4)	13 (4.1)
phototherapy	5 (4.5)	7 (2.2)
psoralen and ultraviolet-A light (PUVA)	1 (0.9)	3 (1.0)

a: number of patients who were included in the safety analysis.
b: within the last 6 months before study inclusion.
c: includes tacrolimus and pimecrolimus.
d: within the last 12 months before study inclusion.
e: includes ciclosporin.
f: includes methotrexate and azathioprine according to the information provided by the company.
g: includes mycophenolate mofetil according to the information provided by the company.
n: number of patients with event; N: number of patients who were included in the safety analysis; PUVA: psoralen and ultraviolet-A light; RCT: randomized controlled trial; TCI: topical calcineurin inhibitors; TCS: topical glucocorticoids; UV: ultraviolet; vs.: versus

The two treatment arms were balanced with regard to prior topical and systemic therapies. Almost 70% of the patients had been treated with high-potency TCS within the last 6 months before study inclusion. About 40% of the patients had received treatment with systemic glucocorticoids within the last 12 months before study inclusion, about 30% received systemic treatment with calcineurin inhibitors. Only a minor proportion of the patients (< 10%) had undergone medical procedures before the start of the study. However, before the start of the study almost twice as many patients had received treatment with selective immunosuppressants in the dupilumab arm vs. the comparator arm.

Risk of bias at study level

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: dupilumab + TCS vs. placebo + TCS

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Personnel			
R668-AD-1224 (CHRONOS[b])	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for the CHRONOS study was rated as low. This concurs with the company's assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - All-cause mortality
- Morbidity
  - Itching, measured with a Peak Pruritus NRS
  - Insomnia recorded with the VAS of the SCORAD
  - Patient-reported symptoms, recorded with the Patient-Oriented Eczema Measure (POEM)

  - Symptomatic relapse
  - Health status, measured with the European Quality of Life-5 Dimensions (EQ-5D) VAS
  - Pain
- Health-related quality of life, measured with the Dermatology Life Quality Index (DLQI)
- Side effects
  - SAEs
  - Discontinuation due to AEs
  - Eye disorders (System Organ Class [SOC])
  - Infections and infestations (SOC)
  - Infections that require treatment with oral antibiotics, antiviral or fungicide drugs for more than 2 weeks (severe infections)
  - General disorders and administration site conditions (SOC)

The results of the second data cut-off (after all randomized patients had received week 52) were used for the benefit assessment. The choice of patient-relevant outcomes and the time point of analysis deviated from that of the company, which used further outcomes and primarily the first data cut-off (see Section 2.3.2).

Table 12 shows for which outcomes data were available in the studies included.

Table 12: Matrix of the outcomes – RCT, direct comparison: dupilumab + TCS vs. placebo + TCS

Study	Outcomes														
	All-cause mortality	**Symptoms (itching – Peak Pruritus NRS)**	**Symptoms (SCORAD-VAS on insomnia)**	**Symptoms (symptomatic relapse)**	**Symptoms (pain)**	**Patient-reported symptoms (POEM)**	**Health status (EQ-5D VAS)**	**Health-related quality of life (DLQI)**	**SAEs**	**Discontinuation due to AEs**	**Eye disorders (SOC)[c]**	**Conjunctivitis (broad CMQ)[c]**	**Infections and infestations (SOC)**	**Infections that require treatment with oral antibiotics, antiviral or fungicide drugs for more than 2 weeks (PT)**	**General disorders and administration site conditions (SOC)**
CHRONOS	Yes	Yes	Yes	No[a]	No[b]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: No usable data.
b: Outcome not recorded in the study.
c: An operationalization on conjunctivitis with 16 PTs specified by the company within the framework of the study is presented as additional information (conjunctivitis broad CMQ). The examination of conjunctivitis events is based on the increased occurrence of conjunctivitis as well as further specified eye diseases under treatment with dupilumab.

AE: adverse event; CMQ: Customized MedDRA query; DLQI: Dermatology Life Quality Index;, EQ-5D: European Quality of Life Group Five Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; NRS: Numerical Rating Scale; POEM: Patient-Oriented Eczema Measure; PT: preferred term; RCT: randomized controlled trial; SCORAD: Scoring Atopic Dermatitis; SOC: System Organ Class; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 13 describes the risk of bias for the relevant outcomes.

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: dupilumab + TCS vs. placebo + TCS

Study		Outcomes														
	Study level	All-cause mortality	Symptoms (itching – Peak Pruritus NRS)	Symptoms (SCORAD-VAS on insomnia)	Symptoms (symptomatic relapse)	Symptoms (pain)	Patient-reported symptoms (POEM)	Health status (EQ-5D VAS)	Health-related quality of life (DLQI)	SAEs	Discontinuation due to AEs	Eye disorders (System Organ Class [SOC])	Conjunctivitis (broad CMQ)	Infections and infestations (SOC)	Infections that require treatment with oral antibiotics, antiviral or fungicide drugs for more than 2 weeks	General disorders and administration site conditions (SOC)
CHRONOS	L	L	H	H	–[a]	-[b]	H[c]	H[c]	H[c]	L	L	L	L	L	L	L

a: No usable data
b: Outcome not recorded in the study
c: Certainty of results is not downgraded (see explanation in the text)

AE: adverse event; CMQ: Customized MedDRA query; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; EQ-5D: European Quality of Life Group Five Dimensions; L: low; MedDRA: Medical Dictionary for Regulatory Activities; NRS: Numerical Rating Scale; POEM: Patient-Oriented Eczema Measure; RCT: randomized controlled trial; SCORAD: Scoring Atopic Dermatitis; SOC: Syst Organ Class; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The risk of bias of the outcomes "all-cause mortality" and all considered side effect outcomes was rated as low. This concurs with the company's assessment.

The risk of bias is rated as high for the outcomes "itching" (Peak Pruritus NRS), "insomnia" (SCORAD-VAS), "patient-reported symptoms" (POEM), "health status" (EQ-5D VAS) and "health-related quality of life" measured with the DLQI. The respective risk of bias results from the violation of the ITT principle caused by a relevant proportion of missing values that differs between the treatment groups.

Since valid sensitivity analyses are available for the symptom outcomes "patient-reported symptoms" (POEM) and "health status" (EQ-5D VAS) as well as "health-related quality of

life", measured with the DLQI, the certainty of results of these outcomes is not downgraded despite the high risk of bias (see Section 2.7.2.4.2 of the full dossier assessment).

This deviates from the assessment of the company insofar as the company assessed the risk of bias as low for all outcomes.

2.4.3 Results

Table 14 and Table 15 summarize the results on the comparison of dupilumab + TCS with placebo + TCS in adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy. Where necessary, Institute's own calculations are provided in addition to the data from the company's dossier.

The derivation of the added benefit of dupilumab in comparison with the ACT is exclusively based on the results obtained after 52 weeks (see Section 2.3.2).

Table 14: Results (mortality, 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					
Mortality					
All-cause mortality	110	0 (0)	315	0 (0)	–
Morbidity					
Symptoms					
Itching – Peak Pruritus NRS improvement by ≥ 4 points[a]	76	53 (69.7)	198	73 (36.9)	1.89 [1.50; 2.39]; < 0.001[b] Sensitivity analysis[d]: 1.64 [1.27; 2.12]
Health-related quality of life					
DLQI (0 or 1)	99	45 (45.5)	264	47 (17.8)	2.55 [1.82; 3.58]; < 0.001[b] Sensitivity analysis[d]: 2.45 [1.74; 3.45]
Side effects					
AEs (supplementary information)	110	101 (91.8)	315	278 (88.3)	–
SAEs	110	4 (3.6)	315	20 (6.3)	0.57 [0.20; 1.64]; 0.302[b]
Discontinuation due to AEs	110	3 (2.7)	315	26 (8.3)	0.33 [0.10; 1.07]; 0.049[b, c]
Eye disorders	110	33 (30.0)	315	46 (14.6)	2.05 [1.39; 3.04]; < 0.001[e]
Conjunctivitis (broad CMQ)[f] (presented as supplementary information)	110	27 (24.5)	315	35 (11.1)	2.21 [1.40; 3.47]; < 0.001[e]
Infections and infestations	110	68 (61.8)	315	188 (59.7)	1.04 [0.87; 1.23]; 0.740[e]
Infections that require treatment with oral antibiotics, antiviral or fungicide drugs for more than 2 weeks	110	1 (0.9)	315	6 (1.9)	0.48 [0.06; 3.92]; 0.594[e]
General disorders and administration site conditions	110	29 (26.4)	315	53 (16.8)	1.57 [1.05; 2.33]; 0.033[e]

(continued)

Table 14: Results (mortality, morbidity; health-related quality of life, side effects, dichotomous) – RCT, direct comparison: dupilumab + TCS vs. placebo + TCS (continued)

a: Comparable results for "itching" (Peak Pruritus NRS) improvement by ≥ 3 points: RR [95% CI]: 1.69 [1.40; 2.02].
b: Institute's calculation, unconditional exact test (CSZ method according to [18]).
c: Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
d: Institute's sensitivity analysis: missing values in both treatment arms were imputed according to the proportion of patients with events in the control arm, and a correction of variance was conducted according to the data-set re-sizing approach (approach W3 in [19]).
e: Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [18]).
f: An operationalization on conjunctivitis with 16 PTs specified by the company within the framework of the study is presented as additional information (conjunctivitis broad CMQ). The examination of conjunctivitis events is based on the increased occurrence of conjunctivitis as well as further selected eye diseases under treatment with dupilumab.

AE: adverse event; CI: confidence interval; CMQ: Customized MedDRA query; 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; NRS: Numerical Rating Scale; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TCS: topical glucocorticoids; vs.: versus

Table 15: Results (morbidity, continuous) – RCT, direct comparison: dupilumab + TCS vs. placebo + TCS

Study Outcome category	Dupilumab + TCS			Placebo + TCS			Dupilumab + TCS vs. placebo + TCS
Outcome	**N[a]**	**Values at study start mean (SD)**	**Change at week 52 mean (SE)[b]**	**N[a]**	**Values at study start mean (SD)**	**Change at week 52 mean[b] (SE)**	**MD [95% CI]; p-value[b]**
CHRONOS							
Morbidity							
Symptoms							
Patient-reported symptoms (POEM)[c]	106	20.3 (5.7)	−13.8 (0.66)	315	20.0 (6.0)	−6.7 (0.40)	−7.0 (−8.51; −5.57); < 0.001 Hedges' g[d]: −1.05 [−1.28; −0.81]
Insomnia – SCORAD-VAS	99	5.7 (3.18)	−4.1 (0.19)	263	4.8 (3.29)	−2.9 (0.12)	−1.2 [−1.6; −0.7]; < 0.001 Hedges' g: −0.61 [−0.84; −0.38]
Health status							
EQ-5D VAS[c]	106	57.8 (22.5)	21.4 (1.65)	319	56.5 (23.7)	15.2 (0.97)	6.2 [2.46; 9.85]; < 0.001 Hedges' g[d]: 0.37 [0.15; 0.59]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study (possibly at other time points) may be based on other patient numbers.
b: Calculated using an ANCOVA model; treatment, baseline value, region and severity of the atopic dermatitis (IGA) as factors.
c: Imputation of missing values using MI.
d: Institute's calculation of mean difference and CI.

ANCOVA: analysis of covariance; CI: confidence interval; EQ-5D: European Quality of Life Group Five Dimensions; IGA: Investigator's Global Assessment; 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 glucocorticoids; VAS: visual analogue scale; vs.: versus

Based on the available data, at most indications, e.g. of an added benefit, can be determined for the outcomes presented in Table 14 and Table 15. This deviates from the approach of the company, which derived proof for individual outcomes.

Mortality

All-cause mortality

After 52 weeks, no deaths had occurred in both relevant study arms of the CHRONOS study. This resulted in no hint of an added benefit of dupilumab in comparison with the comparator therapy, an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Symptoms (itching – Peak Pruritus NRS)

For the symptom outcome “itching” (Peak Pruritus NRS), responder analyses were used for an improvement ≥ 4 points at week 52. There was a statistically significant difference in favour of dupilumab in the relevant analysis of the company. This result is confirmed in a sensitivity analysis conducted by the Institute. However, the uncertainty due to the high proportion of missing values amounting to more than 30% is not completely outweighed by the sensitivity analysis. Given the consequential high risk of bias (see Section 2.4.2), there is a hint of an added benefit of dupilumab in comparison with the comparator therapy.

This deviates from the assessment of the company, which used the results at week 16 in addition to those of week 52 and derived proof of an added benefit for this outcome on the basis of the results from the CHRONOS and CAFE studies.

Symptoms: insomnia (SCORAD-VAS)

For the outcome "insomnia", measured with the VAS on “insomnia” of the SCORAD, a statistically significant and relevant difference in favour of dupilumab was shown for the mean change at week 52 versus the start of the study. The standardized mean difference in the form of Hedges’ g was considered to check the relevance of the result. The 95% confidence interval (CI) was completely below the irrelevance threshold of –0.2. This was interpreted to be a relevant effect. However, the risk of bias is high for this outcome, since only the company’s analyses on this outcome without adequate imputation of missing values are available. The reduced certainty of conclusions of the results resulted in a hint of an added benefit of dupilumab in comparison with the comparator therapy.

This deviates from the assessment of the company, which used the results at week 16 in addition to those of week 52 and derived proof of an added benefit for this outcome on the basis of the results from the CHRONOS and CAFE studies.

Patient-reported symptoms (POEM)

For the patient-reported symptoms recorded with the POEM, the mean change between week 52 and the start of the study is considered. There was a statistically significant difference in favour of dupilumab for this outcome. The standardized mean difference in the form of Hedges’ g was considered to check the relevance of the result. The 95% CI was completely below the irrelevance threshold of –0.2. This was interpreted to be a relevant effect. There was an indication of an added benefit of dupilumab in comparison with the comparator therapy.

This deviates from the assessment of the company, which derived proof of an added benefit for this outcome on the basis of a responder analysis and the results of the CHRONOS and CAFE studies. Moreover, the company considered the results at week 16 in addition to the results at week 52.

Health status

For the outcome "health status" (EQ-5D VAS), a statistically significant difference in favour of dupilumab was shown for the mean change at week 52 versus the start of the study. However, the 95% CI of the standardized mean difference (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. As a result, there was no hint of an added benefit of dupilumab versus the comparator therapy for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived proof of an added benefit for this outcome primarily on the basis of a responder analysis and the results from the CHRONOS and CAFE studies. Moreover, the company considered the results at week 16 in addition to those at the time of analysis at week 52.

Health-related quality of life

DLQI

There is a statistically significant difference in favour of dupilumab for the proportion of patients with a DLQI score of 0 or 1 at week 52. This results in an indication of an added benefit of dupilumab versus the comparator therapy.

This deviates from the assessment of the company, which used the results at the time of analysis at week 16 in addition to those at week 52 and derived proof of an added benefit for the DLQI on the basis of the results from the CHRONOS and CAFE studies.

Side effects

Serious adverse events and discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "serious adverse events (SAEs)" after week 52. There was a statistically significant difference for the outcome "discontinuation due to AEs", however, the related effect is assumed to be no more than marginal. Hence, there was no hint of greater or lesser harm of dupilumab in comparison with the comparator therapy for these outcomes. Greater or lesser harm is therefore not proven for these outcomes.

This concurs with the company's assessment, which, however, used the results at the time of analysis at week 16 in addition to those at week 52 and took the results of the CHRONOS and CAFE studies as a basis.

Specific adverse events

Eye disorders (SOC)

A statistically significant difference to the disadvantage of dupilumab was shown for the outcome "eye disorders".

Moreover, the present benefit assessment additionally considered the CMQ (Customized MedDRA queries) conjunctivitis. This was specified post hoc in the CHRONOS study, since increased incidence of conjunctivitis under treatment with dupilumab was observed in the previous phase 3 studies. The CMQ comprises 16 PTs (broad CMQ) providing a more comprehensible reflection of the AE "conjunctivitis" than the SOC "eye diseases": The PTs "conjunctivitis", "bacterial conjunctivitis" and "viral conjunctivitis" are included in the operationalization "conjunctivitis" (broad CMQ), which were not comprised in the SOC "eye diseases" in the CHRONOS study. The results on conjunctivitis (broad CMQ) are comparable with those on the SOC "eye diseases".

Altogether, this results in an indication of greater harm of dupilumab in comparison with the comparator therapy.

This concurs with the company's assessment, which also reached the same conclusion based on the analysis on the outcome "SOC eye diseases" , however, using the results of the CHRONOS and CAFE studies. Moreover, the company considered the results at week 16 in addition to those obtained at the time of analysis at week 52.

Infections and infestations as well as infections that require treatment with oral antibiotics, antiviral or fungicide drugs for more than 2 weeks

No statistically significant difference between the treatment groups was shown for the outcomes "infections and infestations" as well as infections that require treatment with oral antibiotics, antiviral or fungicide drugs for more than 2 weeks. Hence, there was no hint of greater or lesser harm from dupilumab in comparison with the comparator therapy for the outcomes mentioned; greater or lesser harm is therefore not proven.

This concurs with the company's assessment, which is, however, based on the CHRONOS and CAFE studies. Moreover, the company used further operationalizations and considered the results at week 16 in addition to those at the time of analysis at week 52.

General disorders and administration site conditions

A statistically significant difference to the disadvantage of dupilumab was shown for the outcome "general disorders and administration site conditions". However, the effect is no more than marginal. Hence, there was no hint of greater or lesser harm from dupilumab in comparison with the comparator therapy for the outcome mentioned; greater or lesser harm is therefore not proven.

This concurs with the company's assessment, which is, however, based on the results of the CHRONOS and CAFE studies. Moreover, the company considered the results at week 16 in addition to the at the time of analysis at week 52.

The common AEs are presented in Appendix B of the full dossier assessment.

2.4.4 Subgroups and other effect modifiers

The following effect modifiers were considered in the benefit assessment (see Section 2.7.2.2 of the full dossier assessment):

- sex (female/male)
- age (≥ 18 to < 40 years / ≥ 40 to < 65 years / ≥ 65 years)
- Region (Asia-Pacific / Eastern Europe / North and South America / Western Europe)
- Disease severity at the start of the study (IGA = 3 / IGA = 4)

Additionally, itching was considered to be a relevant effect modifier at the start of the study. However, the company did not consider this and accordingly presented no relevant subgroup analyses. The impact of this effect modificator on the results of the CHRONOS study was unclear, since Institute's calculations were not possible on the basis of the available data.

Due to the basically low numbers of events (≤ 10 events), subgroup analyses were not conducted for the adverse event "infections" requiring treatment with oral antibiotics, antiviral or fungicide drugs for more than 2 weeks, which is used for the description of severe courses of infections. This concurs with the company's approach.

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

Altogether, no relevant effect modifications were observed for the considered subgroup characteristics. This concurs with the approach of the company insofar as it also observed no relevant effect modifications on the basis of the considered subgroup characteristics.

Moreover, the company conducted subgroup analyses on the subpopulation of patients with severe atopic dermatitis for whom systemic treatment with ciclosporin is unsuitable (CAFE-like). This subpopulation is not considered separately in the present benefit assessment (for reasons, see Section 2.3.2).

2.5 Probability and extent of added benefit[6]

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes are taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [20].

[6] 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

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

2.5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4.3 (see Table 16).

Determination of the outcome category for the outcomes on "symptoms"

It could not be inferred from Module 4 A of the dossier for all outcomes considered in the present benefit assessment whether they were non-severe/non-serious or severe/serious. The classification of these outcomes is justified below.

Itching

The company assigned the symptom outcome “itching” to the outcome category “severe symptoms/late complications” and justified its approach with the median baselines of the patients’ Peak Pruritus NRS of 7.7 (dupilumab arm) or 7.6 (comparator arm) at the start of the study. The company presented no documents that justify this classification. For this reason, the outcome “itching” was assigned to the outcome category “non-severe symptoms/late complications”, which deviated from the company’s assessment.

Insomnia

The patients’ subjective assessment of the outcome “insomnia” is included in the total score via a VAS [21]. The highest possible value is 10 and represents the maximum severity of the insomnia. Analogous to the assessment of the outcome category of the symptom “itching”, the company used the data available at the start of the study for an assessment of the severity of the symptom “insomnia”. Based on average SCORAD VAS baselines of 5.7 in the dupilumab arm or 4.8 in the comparator arm, the company assigns the outcome “insomnia” to the outcome category “severe symptoms/late complications”. The company presented no documents that justify this classification. For this reason, the outcome “insomnia” was assigned to the outcome category “non-severe symptoms/late complications”, which deviated from the assessment by the company.

Patient-reported symptoms (POEM)

POEM is a questionnaire for the subjective recording of the frequency of the symptoms of atopic dermatitis. Since the POEM only records the frequency and not the severity 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].

symptoms, it is assigned to the outcome category “non-severe symptoms/late complications”. This concurs with the company’s assessment.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 16).

Table 16: Extent of added benefit at outcome level: dupilumab + TCS vs. placebo + TCS

Outcome category **Outcome**	**Dupilumab + TCS vs. placebo + TCS** **Proportion of events (%) or mean change** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality (week 52)	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
Itching – Peak Pruritus NRS, improvement by ≥ 4 points	69.7% vs. 36.9% RR: 1.89 [1.50; 2.39]; p < 0.001 Sensitivity analysis[c] RR: 1.64 [1.27; 2.12] RR: 0.61 [0.47; 0.79][d] Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Added benefit, extent: “considerable”
Insomnia – SCORAD-VAS	−4.1 vs. −2.9 MD: -1.2 [-1.6; -0.7]; p < 0.001 Hedges’ g: -0.61 [-0.84; -0.38] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
Patient-reported symptoms (POEM)	-13.8 vs. -6.7 MD: -7.0 [-8.51; -5.57]; p < 0.001 Hedges’ g: -1.05 [-1.28; -0.81] Probability: "indication”	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
Health status EQ-5D VAS	21.4 vs. 15.2 MD: 6.2 [2.46; 9.85]; p < 0.001 Hedges’ g: 0.37 [0.15; 0.59]	Lesser benefit/added benefit not proven
Health-related quality of life		
DLQI (0 or 1)	45.5% vs. 17.8% RR: 2.55 [1.82; 3.58]; p < 0.001 Sensitivity analysis[c] RR: 2.45 [1.74; 3.45] RR: 0.41 [0.29; 0.57][d] Probability: "indication”	Outcome category: health-related quality of life CI_u < 0.75 Added benefit, extent: “major”

(continued)

Table 16: Extent of added benefit at outcome level: dupilumab + TCS vs. placebo + TCS (continued)

Outcome category **Outcome**	**Dupilumab + TCS vs. placebo + TCS** **Proportion of events (%) or mean change** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
Serious adverse events	3.6% vs. 6.3% RR: 0.57 [0.20; 1.64]; p = 0.302	Greater/lesser harm not proven
Discontinuation due to AEs	2.7% vs. 8.3% RR: 0.33 [0.10, 1.07]; p = 0.049[f]	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u$ Greater/lesser harm not proven[g]
Eye disorders	30.0% vs. 14.6% RR: 2.05 [1.39; 3.04] RR: 0.49 [0.33; 0.72][d] p < 0.001 Probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"
Infections and infestations	61.8% vs. 59.7% RR: 1.04 [0.87; 1.23]; p = 0.740	Greater/lesser harm not proven
Infections requiring treatment with oral antibiotics, antiviral or fungicide drugs for more than 2 weeks	0.9% vs. 1.9% RR: 0.48 [0.06; 3.92]; p = 0.594	Greater/lesser harm not proven
General disorders and administration site conditions	26.4% vs. 16.8% RR: 1.57 [1.05; 2.33] RR: 0.64 [0.43; 0.95][d] p = 0.033	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.0$ Greater/lesser harm not proven[g]

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Institute's sensitivity analysis.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
f: Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

AE: adverse event; CI: confidence interval, CI_o: upper limit of confidence interval; DLQI: Dermatology Life Quality Index; MD: mean difference; NRS: Numerical Rating Scale; POEM: Patient-Oriented Eczema Measure; RR: relative risk; SCORAD: SCORing Atopic Dermatitis; SAE: serious adverse event; TCS: topical glucocorticoids; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of dupilumab + TCS compared with placebo + TCS

Positive effects	Negative effects
Outcome category: non-serious/non-severe symptoms/late complications: ▪ Itching (Peak Pruritus NRS): hint of an added benefit – extent: "considerable" ▪ Patient-reported symptoms (POEM): indication of an added benefit – extent: "non-quantifiable" ▪ Insomnia SCORAD-VAS: hint of an added benefit – extent: "non-quantifiable"	–
Outcome category: "health-related quality of life": ▪ DLQI (0 or 1): indication of an added benefit – extent: "major"	–
–	Outcome category: non-serious/non-severe side effects: ▪ Eye disorders: indication of greater harm – extent "considerable"
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; vs.: versus	

In the overall consideration, there are positive effects of dupilumab in the outcome categories "morbidity" and "health-related quality of life" and a negative effect in the outcome category "side effects".

The positive effects with the extents "considerable" and "major" are contrasted with a negative effect with the extent "considerable". This negative effect does not challenge the positive effects of dupilumab.

Due to the limitations regarding the implementation of the appropriate comparator therapy (see Section 2.3.2), it was unclear how far the observed extent of the effects would have been reached for the individual outcomes after complete implementation of an individually optimized therapy in the comparator group. At the same time, complete elimination of the present effects is not assumed given the proportion of patients whose treatment was potentially not individually optimized (about 16%). In summary, the extent of the added benefit was therefore rated as "non-quantifiable". This results in an indication of a non-quantifiable added benefit of dupilumab in comparison with the ACT for patients with moderate to severe atopic dermatitis who are candidates for systemic treatment.

The result of the assessment of the added benefit of dupilumab in comparison with the ACT is summarized in Table 18.

Table 18: Dupilumab – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with moderate to severe atopic dermatitis who are candidates for systemic treatment	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 glucocorticoids of the classes 2 to 4 ▪ tacrolimus (topical) ▪ UV therapy (UVA[b] / NB-UVB) ▪ systemic glucocorticoids (only short-term within the framework of a relapse treatment) ▪ ciclosporin	Indication of a non-quantifiable added benefit
a: Presentation of the ACT specified by the G-BA. For the implementation of the ACT, the G-BA emphasized the assumption that other, alternative drugs would be used in case of intolerances; that neither the exclusion of topical and/or systemic therapies for the treatment of the atopic dermatitis nor unchanged continuation of inadequate (pre)treatment were adequate implementations of the appropriate comparator therapy. The G-BA described that adjustment of the therapy during the relapses was assumed and was to be differentiated from therapy adjustment during the chronic phases, however, it was not to be considered an individually optimized treatment regimen within the framework of the envisaged therapeutic indication. Besides the treatment of the relapses, adjustment of the treatment should also be possible during the chronic phases within the framework of the study. b: UVA1 is not comprised, because it was excluded. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); UVA: ultraviolet-A light;		

The assessment described above deviates from that of the company, which derived proof of major added benefit based on the results of the CHRONOS and CAFE studies.

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

2.6 List of included studies

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

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: study R668-AD-1224; statistical analysis plan amendment 1 [unpublished]. 2016.

Regeneron Pharmaceuticals. Study to assess the efficacy and long-term safety of dupilumab (REGN668/SAR231893) in adult patients with moderate-to-severe atopic dermatitis (CHRONOS): full text view [online]. In: ClinicalTrials.gov. 17.10.2017 [Accessed: 26.01.2018]. URL: https://clinicaltrials.gov/ct2/show/study/NCT02260986.

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