# Dupilumab
# (eosinophilic oesophagitis, 1 to 11 years)

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

**EXTRACT**

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Dupilumab (eosinophile Ösophagitis, 1 bis 11 Jahre) – Nutzenbewertung gemäß § 35a SGB V*. 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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Dupilumab, Eosinophilic Esophagitis, Infant, Child, Benefit Assessment

**Medical and scientific advice**

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

**Patient and family involvement**

The questionnaire on the disease and its treatment was answered by Klaus-Peter Zimmer.

IQWiG thanks the respondent and the patient organization 'Arbeitsgemeinschaft Allergiekrankes Kind Hilfen für Kinder mit Asthma, Ekzem oder Heuschnupfen (AAK) e. V.' for participating in the written exchange and for their support. The respondent and the 'Arbeitsgemeinschaft Allergiekrankes Kind Hilfen für Kinder mit Asthma, Ekzem oder Heuschnupfen (AAK) e. V.' were not involved in the actual preparation of the dossier assessment.

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# Part I: Benefit assessment

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

# I List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| DGVS | Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten<br>(German Society of Gastroenterology, Digestive and Metabolic Diseases) |
| EoE | eosinophilic oesophagitis |
| eos | eosinophilic |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| hpf | high power field |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen<br>(Institute for Quality and Efficiency in Health Care) |
| PPI | proton pump inhibitor |
| RCT | randomized controlled trial |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SPC | Summary of Product Characteristics |
| TCS | topical corticosteroids |

## I 1 Executive summary of the benefit assessment

### Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug dupilumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 29 November 2024.

### Research question

The aim of this report is to assess the added benefit of dupilumab compared with the appropriate comparator therapy (ACT) in children 1 to 11 years of age, weighing at least 15 kg, with eosinophilic oesophagitis (EoE) who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.

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

Table 2: Research question of the benefit assessment of dupilumab

| **Therapeutic indication** | **ACT**[a] |
|---|---|
| Children 1 to 11 years of age, weighing at least 15 kg, with EoE who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy | Treatment of physician's choice selecting from budesonide or PPI[b] |

a. Presented is the ACT specified by the G-BA.
b. Comments of the G-BA:

- In principle, the recommendation is that if an active EoE is detected, induction therapy should first be initiated as high-dose therapy with budesonide or PPI. The efficacy of any induction therapy should be closely evaluated clinically as well as endoscopically and histologically after a period of 8 to 12 weeks. When a clinical and histological remission is achieved, the medicinal therapy should be continued at a lower dosage than the induction therapy as part of long-term maintenance treatment. In case of relapse, it is recommended to re-initiate induction therapy. In case of non-response, unless a clinical and histological remission is achieved, therapy should be switched. In individual cases of non-response and persistent histological activity, combination therapy of budesonide and PPI, possibly with dietary adherence may be indicated.
- In children 1 to 11 years of age, off-label budesonide and PPI 2 are treatment options that have already been established in health care and that have been shown to be effective and well tolerated in the treatment of EoE based on evidence-based [1-12] guidelines [13-17] as well as practical clinical experience. There are no approved treatment options available for children 1 to 11 years of age. According to §6 (2) sentence 3, number 1 AM-NutzenV, it is therefore appropriate to determine the off-label use of drugs as ACT for this patient population.
- It is assumed that children receive adequate treatment of EoE in accordance with guideline recommendations as part of their treatment of physician's choice.
- If the children enrolled should also include patients who have not yet received therapy with budesonide, or also those who respond to therapy with budesonide, it can be assumed that treatment with budesonide can be suitable for these children in accordance with the guideline recommendations.
- Any therapy adjustment required by the children for the treatment of EoE should be possible in both arms of a clinical study.
- Endoscopic dilatation treatment is assumed to be used sporadically in refractory cases and the presence of strictures. Endoscopic dilatation is therefore not considered a regular comparator, but should be offered for complications in both arms, for example.
- If elimination diets or avoidance diets achieved reduction of symptoms, e.g. in the context of allergic reactions to certain foods, it is assumed that these will be continued. In view of the fact that permanent elimination diets go hand in hand with restrictions in a balanced diet that meets needs, elimination diets are not considered as the sole therapy.
- A single-comparator study is generally insufficient for implementing ACT of physician's choice in a study of direct comparison. The investigator is expected to have a choice between several treatment options (multi-comparator study). A rationale must be provided for the choice and any limitation of treatment options.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; G-BA: Federal Joint Committee; PPI: proton pump inhibitor

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

**Results**

The check did not identify any relevant studies for assessing the added benefit of dupilumab in comparison with the ACT.

In Module 4 K, the company presented the pivotal study EE-1877 (hereinafter referred to as the EoE KIDS study) as supplementary information and derived medical benefit and added benefit from it. However, it described that the study is not suitable for the assessment of added benefit according to the criteria of the G-BA due to the study duration of only 16 weeks.

The data of the EoE KIDS study presented by the company are not suitable for the benefit assessment of dupilumab versus the ACT for the following reasons.

***Study duration too short***

The randomized treatment phase for the potentially relevant comparison of dupilumab with placebo (Study Part A of the EoE KIDS study) lasted 16 weeks. EoE is a chronic disease. According to the Summary of Product Characteristics (SPC), dupilumab is intended for long-term treatment. Therefore, a comparative treatment duration of at least 24 weeks is required to assess the added benefit. The comparative treatment duration of the EoE KIDS study is therefore too short to address the research question of the present benefit assessment.

***No adequate therapy in the comparator arm***

The research question of the present benefit assessment comprises children 1 to 11 years of age, weighing at least 15 kg, with EoE who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy. According to the S2k guideline, conventional drug therapy includes proton pump inhibitors (PPIs) and topical corticosteroids (TCS). The ACT specified by the G-BA for these children is treatment of physician's choice, selecting from the TCS budesonide and PPIs.

In Study Parts A and B of the EoE KIDS study, treatment with TCS was only possible in the context of a rescue treatment, which is a relevant hurdle. The proportion of children who had responded inadequately to TCS in the past, or who had an intolerance or contraindication, was 44% in the placebo arm and 62% in the higher exposure dupilumab arm. This means that 56% of the children in the placebo arm did not meet these criteria and TCS, such as budesonide, would have been an option as treatment of physician's choice. However, the fact that no child ultimately received rescue treatment is not sufficient proof that the children in the study received the best possible treatment in accordance with the ACT.

Treatment with PPIs was also restricted in the EoE KIDS study. Patients who were on PPIs during the screening period had the choice either to remain on the PPI regimen or stop the PPI regimen prior to randomization. Initiation, change in the dosage regimen, or discontinuation of PPIs were not allowed according to the study protocol. As a result, PPIs

were not available during the study to 68% of the children in the placebo arm and 46% of the children in the higher exposure dupilumab arm of the EoE KIDS study. It is unclear to what extent re-initiated PPI treatment for symptom relief would have been indicated for these children during the study period. The remaining 32% of children in the placebo arm and 54% of children in the higher exposure dupilumab arm had to continue their PPI regimen unchanged according to protocol, which does not correspond to the procedure recommended in the S2k guideline.

In the EoE KIDS study, children who had been on an elimination diet for at least 6 weeks at the time of screening had to remain on the same diet throughout the entire study without any changes (this applied to 79% of children in the placebo arm and 87% of children in the higher exposure dupilumab arm). Initiation of an elimination diet was prohibited, which is also not in line with the recommendations of the S2k guideline.

In summary, the EoE KIDS study did not provide for treatment optimization – particularly with TCS – for the children in the placebo arm. This is not considered adequate in view of the fact that the children had active EoE and there were still options for optimizing treatment. In summary, treatment in the placebo arm cannot be classified as adequate, and therefore the ACT was not implemented for the children in the placebo arm of the EoE KIDS study.

***High proportion of children in the dupilumab arm not treated in compliance with the approval***

14% of the children in the higher exposure dupilumab arm weighed between 5 and < 15 kg and were therefore treated off-label. In addition, children weighing 40 kg or more were notably underdosed in the higher exposure dupilumab arm. The company did not provide any information on the proportion of children weighing 40 kg or more.

***Summary***

The EoE KIDS study is not considered suitable for the assessment of the added benefit of dupilumab in the present therapeutic indication because the treatment duration of 16 weeks in Study Part A of the EoE KIDS study was too short and because treatment in the comparator arm was inadequate (not in compliance with the ACT). In addition, a potentially relevant proportion of children in the analyses presented by the company were not treated in compliance with the approval.

**Results on added benefit**

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of dupilumab in comparison with the ACT; an added benefit is therefore not proven.

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

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

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [18,19].

Table 3: Dupilumab – probability and extent of added benefit

| **Therapeutic indication** | **ACT[a]** | **Probability and extent of added benefit** |
|---|---|---|
| Children 1 to 11 years of age, weighing at least 15 kg, with EoE who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy | Treatment of physician's choice selecting from budesonide or PPI[b] | Added benefit not proven |

a. Presented is the ACT specified by the G-BA.
b. Comments of the G-BA:

- In principle, the recommendation is that if an active EoE is detected, induction therapy should first be initiated as high-dose therapy with budesonide or PPI. The efficacy of any induction therapy should be closely evaluated clinically as well as endoscopically and histologically after a period of 8 to 12 weeks. When a clinical and histological remission is achieved, the medicinal therapy should be continued at a lower dosage than the induction therapy as part of long-term maintenance treatment. In case of relapse, it is recommended to re-initiate induction therapy. In case of non-response, unless a clinical and histological remission is achieved, therapy should be switched. In individual cases of non-response and persistent histological activity, combination therapy of budesonide and PPI, possibly with dietary adherence may be indicated.
- In children 1 to 11 years of age, off-label budesonide and PPI 2 are treatment options that have already been established in health care and that have been shown to be effective and well tolerated in the treatment of EoE based on evidence-based [1-12] guidelines [13-17] as well as practical clinical experience. There are no approved treatment options available for children 1 to 11 years of age. According to §6 (2) sentence 3, number 1 AM-NutzenV, it is therefore appropriate to determine the off-label use of drugs as ACT for this patient population.
- It is assumed that children receive adequate treatment of EoE in accordance with guideline recommendations as part of their treatment of physician's choice.
- If the children enrolled should also include patients who have not yet received therapy with budesonide, or also those who respond to therapy with budesonide, it can be assumed that treatment with budesonide can be suitable for these children in accordance with the guideline recommendations.
- Any therapy adjustment required by the children for the treatment of EoE should be possible in both arms of a clinical study.
- Endoscopic dilatation treatment is assumed to be used sporadically in refractory cases and the presence of strictures. Endoscopic dilatation is therefore not considered a regular comparator, but should be offered for complications in both arms, for example.
- If elimination diets or avoidance diets achieved reduction of symptoms, e.g. in the context of allergic reactions to certain foods, it is assumed that these will be continued. In view of the fact that permanent elimination diets go hand in hand with restrictions in a balanced diet that meets needs, elimination diets are not considered as the sole therapy.
- A single-comparator study is generally insufficient for implementing ACT of physician's choice in a study of direct comparison. The investigator is expected to have a choice between several treatment options (multi-comparator study). A rationale must be provided for the choice and any limitation of treatment options.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; G-BA: Federal Joint Committee; PPI: proton pump inhibitor

The G-BA decides on the added benefit.

## I 2 Research question

The aim of this report is to assess the added benefit of dupilumab compared with the ACT in children 1 to 11 years of age, weighing at least 15 kg, with EoE who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.

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

Table 4: Research question of the benefit assessment of dupilumab

| **Therapeutic indication** | **ACT[a]** |
|---|---|
| Children 1 to 11 years of age, weighing at least 15 kg, with EoE who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy | Treatment of physician's choice selecting from budesonide or PPI[b] |

a. Presented is the ACT specified by the G-BA.
b. Comments of the G-BA:

- In principle, the recommendation is that if an active EoE is detected, induction therapy should first be initiated as high-dose therapy with budesonide or PPI. The efficacy of any induction therapy should be closely evaluated clinically as well as endoscopically and histologically after a period of 8 to 12 weeks. When a clinical and histological remission is achieved, the medicinal therapy should be continued at a lower dosage than the induction therapy as part of long-term maintenance treatment. In case of relapse, it is recommended to re-initiate induction therapy. In case of non-response, unless a clinical and histological remission is achieved, therapy should be switched. In individual cases of non-response and persistent histological activity, combination therapy of budesonide and PPI, possibly with dietary adherence may be indicated.
- In children 1 to 11 years of age, off-label budesonide and PPI 2 are treatment options that have already been established in health care and that have been shown to be effective and well tolerated in the treatment of EoE based on evidence-based [1-12] guidelines [13-17] as well as practical clinical experience. There are no approved treatment options available for children 1 to 11 years of age. According to §6 (2) sentence 3, number 1 AM-NutzenV, it is therefore appropriate to determine the off-label use of drugs as ACT for this patient population.
- It is assumed that children receive adequate treatment of EoE in accordance with guideline recommendations as part of their treatment of physician's choice.
- If the children enrolled should also include patients who have not yet received therapy with budesonide, or also those who respond to therapy with budesonide, it can be assumed that treatment with budesonide can be suitable for these children in accordance with the guideline recommendations.
- Any therapy adjustment required by the children for the treatment of EoE should be possible in both arms of a clinical study.
- Endoscopic dilatation treatment is assumed to be used sporadically in refractory cases and the presence of strictures. Endoscopic dilatation is therefore not considered a regular comparator, but should be offered for complications in both arms, for example.
- If elimination diets or avoidance diets achieved reduction of symptoms, e.g. in the context of allergic reactions to certain foods, it is assumed that these will be continued. In view of the fact that permanent elimination diets go hand in hand with restrictions in a balanced diet that meets needs, elimination diets are not considered as the sole therapy.
- A single-comparator study is generally insufficient for implementing ACT of physician's choice in a study of direct comparison. The investigator is expected to have a choice between several treatment options (multi-comparator study). A rationale must be provided for the choice and any limitation of treatment options.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; G-BA: Federal Joint Committee; PPI: proton pump inhibitor

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks are used for deriving any added benefit. This concurs with the company's inclusion criteria.

## I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on dupilumab (status: 17 October 2024)
- bibliographical literature search on dupilumab (last search on 17 October 2024)
- search in trial registries/trial results databases for studies on dupilumab (last search on 17 October 2024)
- search on the G-BA website for dupilumab (last search on 17 October 2024)

To check the completeness of the study pool:

- search in trial registries for studies on dupilumab (last search on 10 December 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any relevant studies for assessing the added benefit of dupilumab in comparison with the ACT. This concurs with the company's assessment.

In Module 4 K, the company presented the pivotal study EE-1877 (hereinafter referred to as the EoE KIDS study) [20] as supplementary information and derived medical benefit and added benefit from it. However, it described that the study is not suitable for the assessment of added benefit according to the criteria of the G-BA due to the study duration of only 16 weeks.

The data of the EoE KIDS study presented by the company are not suitable for the benefit assessment of dupilumab versus the ACT. The EoE KIDS study is described below, followed by an explanation of why the study presented by the company is not suitable for the present benefit assessment.

**Evidence presented by the company – EoE KIDS study**

The randomized EoE KIDS study consists of 3 study parts: Study Part A is a 16-week randomized, double-blind comparison of dupilumab in different dosing regimens ("higher exposure" and "lower exposure", each based on body weight) with placebo. After completing Study Part A, in Study Part B, children in both study arms received dupilumab for 36 weeks with the dosing regimen assigned at randomization (adjustments based on increased weight were possible). In Study Part C, the children could receive dupilumab in an open-label higher exposure regimen for up to 108 weeks.

The EoE KIDS study included children 1 to 11 years of age with active EoE. In the month prior to screening, children had to have a history of symptoms determined by the investigator to be

the result of EoE. Furthermore, the children had to have responded inadequately to PPI treatment already before randomization. This had to be documented by endoscopic biopsy with ≥ 15 intraepithelial eosinophilic (eos)/high power field (hpf) from at least one oesophageal region and performed after at least 8 weeks of treatment with a PPI regimen. If the patient discontinued PPI therapy, the biopsy must have been performed within 2 weeks of the date of discontinuation. If a prior endoscopic biopsy meeting these criteria was not available, the children received treatment with a PPI regimen for at least 8 weeks during the screening period before their endoscopic biopsy planned for all study participants before randomization.

Children with a body weight of < 5 kg or ≥ 60 kg at screening and children with any oesophageal stricture unable to be passed with a standard endoscope or any critical oesophageal stricture that required dilation were excluded from the study. Also excluded were children who were treated with swallowed TCS within 8 weeks prior to endoscopic biopsy scheduled before randomization, or children who initiated, discontinued or changed the dosage regimen of PPIs, leukotriene antagonists and nasal and/or inhaled corticosteroids during this period. In addition, children who had initiated or changed an elimination diet in the 6 weeks prior to screening were also excluded from participation in the study.

Children who were on PPIs during the screening period had the choice either to remain on the PPI regimen during Study Parts A and B or stop the PPI regimen prior to randomization and not re-initiate PPIs during Study Parts A and B. The use of swallowed TCS and systemic corticosteroids was prohibited during Study Parts A and B (except as rescue treatment). Nasal or inhaled corticosteroids or leukotriene antagonists were allowed to be continued in stable doses during Study Parts A and B. Children who were on an elimination diet at the time of screening had to continue this diet unchanged during the study. If medically necessary, e.g. for treatment of intolerable EoE symptoms, rescue medications (systemic corticosteroids and/or TCS) or emergency oesophageal dilations were allowed.

After a screening phase of up to 12 weeks, 102 children in Study Part A received either dupilumab or a corresponding placebo for 16 weeks in the following regimens based on body weight:

- Lower exposure dupilumab arm:
  - ≥ 5 kg to < 15 kg: 200 mg every 4 weeks
  - ≥ 15 kg to < 30 kg: 300 mg every 4 weeks
  - ≥ 30 kg to < 60 kg: 200 mg every 2 weeks
- Higher exposure dupilumab arm:
  - ≥ 5 kg to < 15 kg: 100 mg every 2 weeks

- ≥ 15 kg to < 30 kg: 200 mg every 2 weeks
- ≥ 30 kg to < 60 kg: 300 mg every 2 weeks

The dosing regimen for the body weights ≥ 15 kg to < 30 kg in the higher exposure dupilumab arm corresponds to the dosing according to the SPC [21,22]. All other dosing regimens deviated from the information in the SPC.

Randomization of the children was stratified according to body weight at baseline (≥ 5 kg to < 15 kg versus ≥ 15 kg to < 30 kg versus ≥ 30 kg to < 60 kg).

The primary outcome of the EoE KIDS study was the proportion of children achieving peak oesophageal intraepithelial eosinophil count of ≤ 6 eos/hpf at Week 16. Secondary outcomes included outcomes from the categories of morbidity, health-related quality of life and side effects.

**The EoE KIDS study is unsuitable for the assessment of added benefit**

***Study duration too short***

The randomized treatment phase for the potentially relevant comparison of dupilumab with placebo (Study Part A of the EoE KIDS study) lasted 16 weeks. EoE is a chronic disease. According to the SPC, dupilumab is intended for long-term treatment. Therefore, a comparative treatment duration of at least 24 weeks is required to assess the added benefit. The comparative treatment duration of the EoE KIDS study is therefore too short to address the research question of the present benefit assessment.

***No adequate therapy in the comparator arm***

The research question of the present benefit assessment comprises children 1 to 11 years of age, weighing at least 15 kg, with EoE who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy. According to the S2k guideline, conventional medicinal therapy includes PPIs and TCS [16]. The ACT specified by the G-BA for these children is treatment of physician's choice, selecting from the TCS budesonide and PPIs.

In Study Parts A and B of the EoE KIDS study, treatment with TCS was only possible in the context of a rescue treatment. 79% of children in the placebo arm and 76% of children in the higher exposure dupilumab arm had already received TCS in the past. 62% of children in the placebo arm and 68% of children in the higher exposure dupilumab arm had already received the TCS budesonide in particular. The proportion of children who had responded inadequately to TCS, or who had an intolerance or contraindication, was 44% in the placebo arm and 62% in the higher exposure dupilumab arm. This means that 56% of the children in the placebo arm did not meet these criteria and TCS, such as budesonide, would have been an option as treatment of physician's choice. In addition, treatment with budesonide, possibly in

combination with PPIs, could still be an option for some children with an inadequate response to TCS. However, according to the study protocol in the EoE KIDS study, treatment with budesonide was only permitted as rescue medication, e.g. for intolerable symptoms, which is a relevant hurdle. Therefore, the fact that no child ultimately received rescue treatment is not sufficient proof that the children in the study received the best possible treatment in accordance with the ACT.

Treatment with PPIs was also restricted in the EoE KIDS study. Patients who were on PPIs during the screening period had the choice either to remain on the PPI regimen or stop the PPI regimen prior to randomization. Initiation, change in the dosage regimen, or discontinuation of PPIs were not allowed according to the study protocol. As a result, PPIs were not available during the study to 68% of the children in the placebo arm and 46% of the children in the higher exposure dupilumab arm of the EoE KIDS study. It is unclear to what extent re-initiated PPI treatment for symptom relief would have been indicated for these children during the study period. The remaining 32% of children in the placebo arm and 54% of children in the higher exposure dupilumab arm had to continue their PPI regimen unchanged according to protocol. The current S2k guideline 'Gastroesophageal reflux disease and eosinophilic esophagitis' of the German Society of Gastroenterology, Digestive and Metabolic Diseases (DGVS) recommends high-dose PPI therapy to induce remission. Treatment should be re-evaluated after 8 to 12 weeks and changed if there is no response [16]. However, such re-evaluation of PPI treatment did not take place during the 16-week EoE KIDS study.

In the EoE KIDS study, children who had been on an elimination diet for at least 6 weeks at the time of screening had to remain on the same diet throughout the entire study without any changes (this applied to 79% of children in the placebo arm and 87% of children in the higher exposure dupilumab arm). Initiating an elimination diet was prohibited. The children therefore had to continue the elimination diet unchanged, regardless of whether the current elimination diet reduced their symptoms in the long term. This does not comply with the recommendations of the S2k guideline. For the elimination diet as part of induction therapy or after a change of therapy, however, a re-evaluation should be carried out after 8 to 12 weeks, and guidance by an experienced nutritionist is recommended to avoid malnutrition and eating disorders [16].

In summary, the EoE KIDS study did not provide for treatment optimization – particularly with TCS – for the children in the placebo arm. This is not considered adequate in view of the fact that the children had active EoE and there were still options for optimizing treatment. In summary, treatment in the placebo arm cannot be classified as adequate, and therefore the ACT was not implemented for the children in the placebo arm of the EoE KIDS study.

***High proportion of children in the dupilumab arm not treated in compliance with the approval***

In Module 4 K, the company used the results of the higher exposure dupilumab arm, as the dosing regimens in this arm at least partially corresponded to the approval. Children with a body weight of 5 kg to < 60 kg at screening were included in the EoE KIDS study. However, dupilumab is only approved for children weighing at least 15 kg [21,22]. 14% of the children in the higher exposure dupilumab arm weighed between 5 and < 15 kg and were therefore treated off-label. In addition, children weighing 40 kg or more were notably underdosed in the higher exposure dupilumab arm. In the study, children weighing ≥ 30 kg to < 60 kg received 300 mg dupilumab every 2 weeks. However, children weighing 40 kg or more should receive 300 mg dupilumab once a week according to the SPC [21,22]. The company did not provide any information on the proportion of children weighing 40 kg or more. The higher exposure dupilumab arm of the study thus included a potentially relevant proportion of children who were not treated in compliance with the approval.

***Summary***

The EoE KIDS study is not considered suitable for the assessment of the added benefit of dupilumab in the present therapeutic indication because the treatment duration of 16 weeks in Study Part A of the EoE KIDS study was too short and because treatment in the comparator arm was inadequate (not in compliance with the ACT). In addition, a potentially relevant proportion of children in the analyses presented by the company were not treated in compliance with the approval.

## I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of dupilumab compared with the ACT in children 1 to 11 years of age, weighing at least 15 kg, with EoE who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy. There is no hint of an added benefit of dupilumab in comparison with the ACT; an added benefit is therefore not proven.

## I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of dupilumab in comparison with the ACT is summarized in Table 5.

Table 5: Dupilumab – probability and extent of added benefit

| **Therapeutic indication** | **ACT[a]** | **Probability and extent of added benefit** |
|---|---|---|
| Children 1 to 11 years of age, weighing at least 15 kg, with EoE who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy | Treatment of physician's choice selecting from budesonide or PPI[b] | Added benefit not proven |

a. Presented is the ACT specified by the G-BA.
b. Comments of the G-BA:

- In principle, the recommendation is that if an active EoE is detected, induction therapy should first be initiated as high-dose therapy with budesonide or PPI. The efficacy of any induction therapy should be closely evaluated clinically as well as endoscopically and histologically after a period of 8 to 12 weeks. When a clinical and histological remission is achieved, the medicinal therapy should be continued at a lower dosage than the induction therapy as part of long-term maintenance treatment. In case of relapse, it is recommended to re-initiate induction therapy. In case of non-response, unless a clinical and histological remission is achieved, therapy should be switched. In individual cases of non-response and persistent histological activity, combination therapy of budesonide and PPI, possibly with dietary adherence may be indicated.
- In children 1 to 11 years of age, off-label budesonide and PPI 2 are treatment options that have already been established in health care and that have been shown to be effective and well tolerated in the treatment of EoE based on evidence-based [1-12] guidelines [13-17] as well as practical clinical experience. There are no approved treatment options available for children 1 to 11 years of age. According to §6 (2) sentence 3, number 1 AM-NutzenV, it is therefore appropriate to determine the off-label use of drugs as ACT for this patient population.
- It is assumed that children receive adequate treatment of EoE in accordance with guideline recommendations as part of their treatment of physician's choice.
- If the children enrolled should also include patients who have not yet received therapy with budesonide, or also those who respond to therapy with budesonide, it can be assumed that treatment with budesonide can be suitable for these children in accordance with the guideline recommendations.
- Any therapy adjustment required by the children for the treatment of EoE should be possible in both arms of a clinical study.
- Endoscopic dilatation treatment is assumed to be used sporadically in refractory cases and the presence of strictures. Endoscopic dilatation is therefore not considered a regular comparator, but should be offered for complications in both arms, for example.
- If elimination diets or avoidance diets achieved reduction of symptoms, e.g. in the context of allergic reactions to certain foods, it is assumed that these will be continued. In view of the fact that permanent elimination diets go hand in hand with restrictions in a balanced diet that meets needs, elimination diets are not considered as the sole therapy.
- A single-comparator study is generally insufficient for implementing ACT of physician's choice in a study of direct comparison. The investigator is expected to have a choice between several treatment options (multi-comparator study). A rationale must be provided for the choice and any limitation of treatment options.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; G-BA: Federal Joint Committee; PPI: proton pump inhibitor

The assessment described above deviates from that by the company, which derived a hint of a non-quantifiable added benefit.

The G-BA decides on the added benefit.

## I 6 References for English extract

Please see full dossier assessment for full reference list.

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