IQWiG Reports – Commission No. A22-46

Dupilumab (asthma in children 6 to 11 years old) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Dupilumab (Asthma bei Kindern zwischen 6 und 11 Jahren) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 9 September 2022). 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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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

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

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

List of abbreviations

Abbreviation	Meaning
ACQ-5-IA	Asthma Control Questionnaire 5-item version Interviewer Administered
ACT	appropriate comparator therapy
EPAR	European Public Assessment Report
FeNO	fraction of exhaled nitric oxide
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GINA	Global Initiative for Asthma
ICS	inhaled corticosteroids
IgE	immunoglobulin E
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IU	international units
LABA	long-acting beta-2 agonist
LAMA	long-acting muscarinic antagonist
LTRA	leukotriene receptor antagonist
NVL	Nationale VersorgungsLeitlinie (National Care Guideline)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug dupilumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 19 April 2022.

Research question

The aim of the present report is to assess the added benefit of dupilumab as add-on maintenance treatment in comparison with the appropriate comparator therapy (ACT) in children 6 to 11 years old with severe asthma with type 2 inflammation who are inadequately controlled with medium- to high-dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

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 between 6 and 11 years of age with severe asthma with type 2 inflammation[b] which is not properly controlled despite moderate-to-high-dose ICS plus one further drug as maintenance treatment[c]	Individual treatment escalation[d, e] under consideration of the prior therapy choosing from: ▪ high-dose ICS and LABA and possibly LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[f]

a. Presented is the ACT specified by the G-BA.
b. Characterized by raised blood eosinophils and/or raised FeNO.
c. In view of the wording of the therapeutic indication (severe asthma), it is assumed in accordance with the G-BA that therapy with dupilumab is only indicated in addition to high-dose ICS and at least one other drug for maintenance treatment or in addition to medium-dose ICS and montelukast and LABA and LAMA.
d. According to the G-BA, the stepwise approach to drug therapy of the 2020 NVL for Asthma, 4th edition [1] must be taken into account. It is assumed that, in the therapeutic indication, the patients are represented in steps 5 to 6 of the stepwise approach to drug therapy for children and adolescents. Montelukast is only approved as additional treatment in patients suffering from mild to moderate persistent asthma. Nevertheless, patients with severe asthma who receive montelukast in compliance with the recommendation of the 2020 NVL for Asthma in the present therapeutic indication can be included in the population relevant to the benefit assessment.
e. Unchanged continuation of inadequate treatment of severe asthma does not comply with an ACT in severe uncontrolled asthma if the option for treatment escalation is still available.
f. If the criteria required for the use of omalizumab are met.

FeNO: fraction of exhaled nitric oxide; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; NVL: National Care Guideline

The company followed the specification of the ACT.

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

Results

No relevant study comparing dupilumab against the ACT in the present therapeutic indication was identified. With its information retrieval, the company identified the RCT EFC14153 (hereinafter referred to as "VOYAGE study") and used this study for the assessment of the added benefit of dupilumab. The VOYAGE study included by the company is not suitable for the assessment of the added benefit of dupilumab in comparison with the ACT because the ACT was not implemented. This is described below.

Evidence presented by the company – VOYAGE study

The VOYAGE study is a randomized, double-blind study on the comparison of dupilumab with placebo. Children 6 to 11 years old with uncontrolled moderate to severe asthma were included. The diagnosis had to have been confirmed for ≥ 12 months based on clinical history, examination and pulmonary function parameters according to the Global Initiative for Asthma (GINA) 2015 guideline. In addition, the included patients had experienced worsening of asthma within the last year with at least one treatment with systemic corticosteroids or hospitalization/emergency room visit.

According to the inclusion criterion, all patients had been on maintenance therapy of medium- or high-dose ICS with second controller medication (long-acting beta-2 agonist [LABA], leukotriene receptor antagonist [LTRA], long-acting muscarinic antagonist [LAMA], or methylxanthine) or high-dose ICS alone for ≥ 3 months with a stable dose for ≥ 1 month prior to screening. The ICS dose categories were classified in accordance with the GINA 2015 guideline.

A total of 408 patients were enrolled in the VOYAGE study. The patients were randomly allocated in a 2:1 ratio either to treatment with dupilumab (N = 273) or to placebo (N = 135). Randomization was stratified by ICS dose (medium dose versus high dose according to GINA 2015 guideline), eosinophil count (< 300 versus ≥ 300 cells/µL), and by region (Latin America, Eastern Europe, Western countries).

Treatment with dupilumab was in compliance with the specifications of the Summary of Product Characteristics (SPC). The patients had to continue their existing stable-dose maintenance therapy described above.

The VOYAGE study comprises a screening phase of 4 weeks, a treatment phase of 52 weeks and – if the patients did not participate in the subsequent open-label 1-year extension study – a follow-up phase of a further 12 weeks. The primary outcome of the study was the annualized rate of severe exacerbation events. Secondary outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Subpopulation of the VOYAGE study presented by the company

In its dossier, the company limited the total population of the VOYAGE study in accordance with the approval to patients with type 2 inflammation defined as an eosinophil count ≥ 150/µL and/or a fraction of exhaled nitric oxide (FeNO) value ≥ 20 ppb at baseline. According to the company, the total population and thus also the subpopulation analysed by the company (N = 350) only includes children with severe asthma. This is not correct, as this subpopulation also includes children who do not have severe asthma as defined by the German National Care Guideline (NVL) for Asthma. From the VOYAGE study, only children with severe asthma on maintenance therapy with high-dose ICS (high dose according to the current 2020 NVL for Asthma) and another controller medication (LABA and/or LTRA) (N = 286) would be relevant to the benefit assessment as the subpopulation of interest. This corresponds to 81.7% of the subpopulation analysed by the company.

Appropriate comparator therapy not implemented in the VOYAGE study

The data of the VOYAGE study presented by the company are not suitable for assessing the added benefit of dupilumab in comparison with the ACT, as the various options specified by the G-BA for individual treatment escalation under consideration of the prior therapy were not implemented in the VOYAGE study.

According to the inclusion criteria, the patients in the VOYAGE study had uncontrolled asthma. This is also reflected in the patient characteristics: Patients in the subpopulation analysed by the company had 2.5 severe asthma exacerbations in the previous year, an Asthma Control Questionnaire 5-item version Interviewer Administered (ACQ-5-IA) score of 2.2 at baseline and 2.5 inhalations of reliever medication within 24 h at baseline (in each case, mean across both study arms). The treatment used before the start of the study was therefore inadequate to achieve the treatment goal of asthma control. In this situation, the guidelines recommend treatment escalation.

In the control arm, no escalation of maintenance therapy was planned at baseline, while patients in the intervention arm received dupilumab as add-on therapy. No therapy escalation of the maintenance therapy was planned in the course of the study either, according to the protocol. Rather, during the course of the study, patients had to continue unchanged treatment with the maintenance therapy they had been receiving for ≥ 3 months and at a stable dose for ≥ 1 month prior to screening. Maintenance therapy consisting of > 2 controller medications was not allowed at any time in the study. Thus, no therapy escalation of the maintenance therapy was possible for the subpopulation of interest with high-dose ICS already at baseline and another controller medication in the control arm, although the following options in compliance with the ACT would have been possible for this patient group.

3rd and 4th controller medication (LABA, LTRA and LAMA)

Escalation with a 3rd or 4th controller medication is indicated in case of inadequate asthma control under maintenance therapy with 2 controller medications according to step 5 of the

NVL for Asthma. It can be assumed that all patients in the subpopulation of interest in the VOYAGE study with inadequate asthma control would have been candidates for escalation with a 3rd or 4th controller medication (LABA, LTRA and/or LAMA).

Additional escalation with omalizumab

According to the ACT specified by the G-BA, administration of omalizumab is another possibility of treatment escalation in immunoglobulin E (IgE)-mediated asthma if the criteria of the approval and the treatment notes are fully met. In the VOYAGE study, omalizumab was not allowed within 130 days prior to screening and during the entire course of the study.

The company determined the proportion of patients eligible for omalizumab to be 28.9% in the control arm of the subpopulation it used (calculation using the current classification of the NVL for Asthma for high-dose ICS). Based on the calculations of the company, it is assumed overall that a relevant number of patients in the control arm would have been eligible for omalizumab as an escalation option according to step 6 of the NVL for Asthma, after the therapy options of step 5 had been exhausted.

Conclusion

In the VOYAGE study, the inadequate therapy was continued unchanged in the control arm at baseline and during the course of the study, although further options for therapy escalation existed. The therapy used in the control arm of the study therefore does not correspond to the current recommendations for therapy escalation in the clinical practice guidelines for asthma and therefore also does not correspond to the ACT specified by the G-BA. The ACT of individual treatment escalation was thus not implemented in the VOYAGE study.

Results on added benefit

The company presented no suitable data for the assessment of the added benefit of dupilumab in comparison with the ACT in children 6 to 11 years old with severe asthma with type 2 inflammation who are inadequately controlled with medium- to high-dose ICS plus another medicinal product for maintenance treatment. This results in no hint of added benefit of dupilumab in comparison with the ACT; an added benefit for these patients 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.

Table 3: Dupilumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Children between 6 and 11 years of age with severe asthma with type 2 inflammation[b] which is not properly controlled despite moderate-to-high-dose ICS plus one further drug as maintenance treatment[c]	Individual treatment escalation[d, e] under consideration of the prior therapy choosing from: ▪ high-dose ICS and LABA and possibly LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[f]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Characterized by raised blood eosinophils and/or raised FeNO.
c. In view of the wording of the therapeutic indication (severe asthma), it is assumed in accordance with the G-BA that therapy with dupilumab is only indicated in addition to high-dose ICS and at least one other drug for maintenance treatment or in addition to medium-dose ICS and montelukast and LABA and LAMA.
d. According to the G-BA, the stepwise approach to drug therapy of the 2020 NVL for Asthma, 4th edition [1] must be taken into account. It is assumed that, in the therapeutic indication, the patients are represented in steps 5 to 6 of the stepwise approach to drug therapy for children and adolescents. Montelukast is only approved as additional treatment in patients suffering from mild to moderate persistent asthma. Nevertheless, patients with severe asthma who receive montelukast in compliance with the recommendation of the 2020 NVL for Asthma in the present therapeutic indication can be included in the population relevant to the benefit assessment.
e. Unchanged continuation of inadequate treatment of severe asthma does not comply with an ACT in severe uncontrolled asthma if the option for treatment escalation is still available.
f. If the criteria required for the use of omalizumab are met.

FeNO: fraction of exhaled nitric oxide; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; NVL: National Care Guideline

The G-BA decides on the added benefit.

[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 [2,3].

2.2 Research question

The aim of the present report is to assess the added benefit of dupilumab as add-on maintenance treatment in comparison with the ACT in children 6 to 11 years old with severe asthma with type 2 inflammation who are inadequately controlled with medium- to high-dose ICS plus another medicinal product for maintenance treatment.

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 between 6 and 11 years of age with severe asthma with type 2 inflammation[b] which is not properly controlled despite moderate-to-high-dose ICS plus one further drug as maintenance treatment[c]	Individual treatment escalation[d, e] under consideration of the prior therapy choosing from: ▪ high-dose ICS and LABA and possibly LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[f]

a. Presented is the ACT specified by the G-BA.
b. Characterized by raised blood eosinophils and/or raised FeNO.
c. In view of the wording of the therapeutic indication (severe asthma), it is assumed in accordance with the G-BA that therapy with dupilumab is only indicated in addition to high-dose ICS and at least one other drug for maintenance treatment or in addition to medium-dose ICS and montelukast and LABA and LAMA.
d. According to the G-BA, the stepwise approach to drug therapy of the 2020 NVL for Asthma, 4th edition [1] must be taken into account. It is assumed that, in the therapeutic indication, the patients are represented in steps 5 to 6 of the stepwise approach to drug therapy for children and adolescents. Montelukast is only approved as additional treatment in patients suffering from mild to moderate persistent asthma. Nevertheless, patients with severe asthma who receive montelukast in compliance with the recommendation of the 2020 NVL for Asthma in the present therapeutic indication can be included in the population relevant to the benefit assessment.
e. Unchanged continuation of inadequate treatment of severe asthma does not comply with an ACT in severe uncontrolled asthma if the option for treatment escalation is still available.
f. If the criteria required for the use of omalizumab are met.

FeNO: fraction of exhaled nitric oxide; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; NVL: National Care Guideline

The company followed the specification of the ACT.

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

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: 10 February 2022)
- bibliographical literature search on dupilumab (last search on 11 February 2022)
- search in trial registries/trial results databases for studies on dupilumab (last search on 11 February 2022)
- search on the G-BA website for dupilumab (last search on 10 February 2022)

To check the completeness of the study pool:

- search in trial registries for studies on dupilumab (last search on 27 April 2022); for search strategies, see Appendix A of the full dossier assessment

No relevant study comparing dupilumab against the ACT in the present therapeutic indication was identified from the check. With its information retrieval, the company identified the RCT EFC14153 (hereinafter referred to as "VOYAGE study") [4-7] and used this study for the assessment of the added benefit of dupilumab.

The VOYAGE study included by the company is not suitable for the assessment of the added benefit of dupilumab in comparison with the ACT because the ACT was not implemented. The following text first provides a description of the VOYAGE study. Subsequently, the population presented by the company is characterized and reasons are given as to why the study is not suitable for assessing the added benefit of dupilumab in comparison with the ACT.

2.3.1 The VOYAGE study presented by the company

Table 5 and Table 6 describe the VOYAGE study.

Table 5: Characteristics of the study included by the company – RCT, direct comparison: dupilumab vs. placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
VOYAGE	RCT, double-blind, parallel	Children 6 to 11 years old with uncontrolled[b] moderate to severe asthma ▪ existing therapy of medium- or high-dose ICS[d] with second controller medication (LABA, LTRA, LAMA, or methylxanthine) or high-dose ICS[d] alone for ≥ 3 months with a stable dose for ≥ 1 month prior to screening ▪ worsening of asthma within the last year with at least one treatment with systemic corticosteroids or hospitalization/emergency room visit	Dupilumab (N = 273) placebo (N = 135) Of which subpopulation with type 2 inflammation[e] analysed by the company: dupilumab (N = 236) placebo (N = 114)	Screening: 4 weeks Treatment[f]: 52 weeks Follow-up[g]: 12 weeks	90 study centres in: Argentina, Australia, Brazil, Canada, Chile, Colombia, Hungary, Italy, Lithuania, Mexico, Poland, Russia, South Africa, Spain, Turkey, Ukraine, USA 4/2017–8/2020	Primary: annualized rate of severe exacerbation events Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include exclusively data on the basis of the information provided by the company's Module 4 F.
b. One of the following criteria had to be fulfilled during the 4(± 1)-week screening period:
- ACQ-5-IA5 score ≥ 1.5 on at least 1 day of the screening period including the visit at randomization
- use of reliever medication (i.e. albuterol/salbutamol, levalbuterol/levosalbutamol), other than as a preventive for exercise induced bronchospasm, on ≥ 3 days/week, in at least 1 week during screening
- nocturnal awakening due to asthma symptoms requiring use of reliever medication at least once during the screening period
- asthma symptoms on ≥ 3 days/week in at least 1 week during screening

c. Asthma diagnosis ≥ 12 months prior to screening based on clinical history, examination and pulmonary function parameters according to the GINA 2015 guideline [8]; pre-bronchodilator FEV1 ≤ 95% of predicted normal or FEV1/FVC ratio < 0.85 at screening and at baseline; reversibility of ≥ 10% in FEV1 after the administration of reliever medication.
d. Dosage category (medium or high dose) according to the GINA 2015 guideline [8].
e. Eosinophil count ≥ 150/µL or FeNO value ≥ 20 ppb at baseline.
f. After the end of the treatment phase, patients could participate in an extension study with dupilumab for 1 year.
g. The follow-up phase after the end of treatment did not take place for patients who participated in the extension study.

ACQ-5-IA: Asthma Control Questionnaire 5-item version Interviewer Administered; AE: adverse event; FeNO: fraction of exhaled nitric oxide; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; N: number of randomized patients; ppb: parts per billion; RCT: randomized controlled trial

Table 6: Characteristics of the intervention – RCT, direct comparison: dupilumab vs. placebo

Study	Intervention	Comparison
VOYAGE	Dupilumab: SC every 2 weeks, based on weight: ▪ ≤ 30 kg BW: 100 mg in a 150 mg/mL prefilled syringe (0.67 mL) ▪ > 30 kg BW: 200 mg in a 175 mg/mL prefilled syringe (1.14 mL) + continuation of the existing maintenance therapy (see information under pretreatment and concomitant treatment)	Placebo: SC every 2 weeks, based on weight: ▪ ≤ 30 kg BW: 0.67 mL ▪ > 30 kg BW: 1.14 mL
	Pretreatment Maintenance therapy[a]: ▪ medium- or high-dose ICS[b] with another controller medication (LABA, LAMA, LTRA, or methylxanthine) ▪ high-dose ICS alone **Permitted concomitant treatment** Maintenance therapy: ▪ continuation of the existing stable-dose maintenance therapy (see pretreatment) ▪ Maintenance therapy could be escalated after ≥ 2 severe asthma exacerbation events: ▫ Patients on high-dose ICS monotherapy[b] could receive a second controller medication. ▫ Patients on a combination of medium-dose ICS[b] and another controller medication could be switched to a combination of high-dose ICS[b] and another controller medication. Reliever medication: ▪ albuterol/salbutamol or levalbuterol/levosalbutamol ▪ In case of asthma deterioration, the ICS dose could be increased up to 4-fold for a maximum of 10 days. Other: ▪ antihistamines ▪ dermatological, ocular or intranasal corticosteroids (except for high-potency dermatological corticosteroids) **Prohibited prior and concomitant treatment** ▪ combination of > 2 controller medications ▪ reliever medication other than albuterol/salbutamol or levalbuterol/levosalbutamol had to be avoided ▪ systemic corticosteroids (except for the treatment of severe exacerbations) or high-potency topical corticosteroids within 30 days prior to screening or during the randomized treatment phase ▪ anti-immunoglobulin E therapy (e.g. omalizumab) within 130 days prior to screening, or any other biologic therapy/immunosuppressant to treat inflammatory disease or autoimmune disease within 2 months or 5 half-lives prior to screening (visit 1), whichever was longer ▪ allergen immunotherapy (except if initiated > 3 months prior to screening and dose stable 1 month prior to screening) ▪ intravenous immunoglobulin therapy ▪ other investigational antibodies within 5 half-lives (in case the half-life is not known, within 6 months) prior to screening	

a. For ≥ 3 months with a stable dose for ≥ 1 month prior to screening.
b. Dosage category (medium or high dose) according to the *Global Strategy for Asthma Management and Prevention* - GINA 2015 [8].

BW: body weight; ICS: inhaled corticosteroids; GINA: Global Initiative for Asthma; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; RCT: randomized controlled trial; SC: subcutaneous

The VOYAGE study is a randomized, double-blind study on the comparison of dupilumab with placebo. Children 6 to 11 years old with uncontrolled moderate to severe asthma were included. The diagnosis had to have been confirmed for ≥ 12 months based on clinical history, examination and pulmonary function parameters according to the GINA 2015 guideline [8]. Evidence of uncontrolled asthma was established with at least one of the following criteria during the 4-week screening period:

- ACQ-5-IA score ≥ 1.5 on at least 1 day, or
- use of reliever medication on ≥ 3 days/week, in at least 1 week, or
- at least one nocturnal awakening due to asthma symptoms requiring use of reliever medication, or
- asthma symptoms on ≥ 3 days/week in at least 1 week.

In addition, the included patients had experienced worsening of asthma within the last year with at least one treatment with systemic corticosteroids or hospitalization/emergency room visit.

According to the inclusion criterion, all patients had been on maintenance therapy of medium- or high-dose ICS with second controller medication (LABA, LTRA, LAMA, or methylxanthine) or high-dose ICS alone for ≥ 3 months with a stable dose for ≥ 1 month prior to screening. The ICS dose categories were classified in accordance with the GINA 2015 guideline [8] (see Section 2.3.2 for information on the ICS dose categories).

A total of 408 patients were enrolled in the VOYAGE study. The patients were randomly allocated in a 2:1 ratio either to treatment with dupilumab (N = 273) or to placebo (N = 135). Randomization was stratified by ICS dose (medium dose versus high dose according to GINA 2015 guideline), eosinophil count (< 300 versus ≥ 300 cells/µL), and by region (Latin America, Eastern Europe, Western countries).

Treatment with dupilumab was in compliance with the specifications of the SPC [9,10]. The patients had to continue their existing stable-dose maintenance therapy described above. Only after at least 2 severe asthma exacerbation events could maintenance therapy be escalated in patients with medium-dose ICS or with high-dose ICS monotherapy. Regardless of this, a short-term increase of the ICS dose up to 4 times the existing dose for a maximum of 10 days was possible if the asthma worsened. Treatment could then be changed to oral corticosteroids or revert back to the original ICS dose. For escalation of the maintenance therapy and the associated check of the implementation of the ACT in the VOYAGE study, see the relevant section below.

The VOYAGE study comprises a screening phase of 4 weeks, a treatment phase of 52 weeks and – if the patients did not participate in the subsequent open-label 1-year extension study – a follow-up phase of a further 12 weeks. The primary outcome of the study was the annualized

rate of severe exacerbation events. Secondary outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

2.3.2 Subpopulation of the VOYAGE study presented by the company

In its dossier, the company limited the total population of the VOYAGE study in accordance with the approval [9,10] to patients with type 2 inflammation defined as an eosinophil count ≥ 150/µL and/or a FeNO value ≥ 20 ppb at baseline. According to the company, the total population and thus also the subpopulation analysed by the company only includes children with severe asthma. This is not correct, as the subpopulation used by the company also includes children who do not have severe asthma as defined by the NVL for Asthma [1]. The European Public Assessment Report (EPAR) [11] and the main publication [5] also describe that patients with moderate to severe asthma were included in the VOYAGE study.

The therapeutic indication for dupilumab in children 6 to 11 years old restricts its use (in addition to the criteria of type 2 inflammation, inadequately controlled with medium- to high-dose ICS plus another medicinal product) to patients with severe asthma. According to the NVL for Asthma, children and adolescents have severe asthma if, with appropriate and adequately conducted therapy with the goal of good asthma control, add-on therapy with a LAMA or a monoclonal antibody must be administered permanently (> 6 months) and/or a high daily dose of ICS is needed [1]. Thus, the definition of severe asthma is linked to the existing maintenance therapy. In accordance with this definition and also with the G-BA notes on the ACT, it is assumed that therapy with dupilumab is only indicated in addition to high-dose ICS and at least one other drug for maintenance treatment or in addition to medium-dose ICS and montelukast and LABA and LAMA (see Table 4).

In order to determine the proportion of patients with severe asthma in the VOYAGE study, the maintenance therapy used is therefore considered below. As the classification of ICS doses into high, medium and low according to the 2015 GINA guideline [8] used in the VOYAGE study is no longer up-to-date, the company recalculated the ICS doses used in the study based on the current NVL for Asthma [1] for the dossier. An important difference in the classification is that the medium dosage of fluticasone propionate according to the GINA 2015 guideline is now considered a high dose according to the NVL for Asthma. Table 7 shows the maintenance therapy at baseline in the subpopulation presented by the company on the basis of the current classification of ICS dose categories according to the NVL for Asthma [1], which is therefore decisive for the benefit assessment.

Table 7: Maintenance therapy in the subpopulation of VOYAGE study included by the company – RCT, direct comparison: dupilumab vs. placebo

Study Characteristic Category	Dupilumab N[a] = 236	Placebo N[a] = 114
VOYAGE		
ICS dose [µg], mean (SD)	502 (262)	484 (265)
High[b], n (%)	200 (85)	95 (83)
Medium[b], n (%)	36 (15)	19 (17)
Low[b], n (%)	0 (0)	0 (0)
High-dose ICS[b] monotherapy, n (%)	8 (3)	1 (< 1)
ICS combination therapies, n (%)		
ICS + LABA	196 (83)	101 (89)
ICS + LTRA	30 (13)	12 (11)
ICS + LTRA + LABA[c]	2 (< 1)	0 (0)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Classification according to the 2020 NVL for Asthma [1].
c. According to the study protocol, treatment with > 2 asthma medications as maintenance therapy was excluded.

ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LTRA: long-acting beta-2 agonist; NVL: National Care Guideline; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation

In the subpopulation of the VOYAGE study presented by the company, no child was treated with a LAMA or a monoclonal antibody at the time of study inclusion. Thus, (according to the definition of the NVL for Asthma and the G-BA notes on the ACT) in this population, only children with a high ICS dose had severe asthma at baseline (295 patients in the subpopulation presented by the company, see Table 7). However, patients with high-dose ICS monotherapy (9 patients in the subpopulation presented by the company, see Table 7) are not included in the therapeutic indication, as dupilumab is only indicated in addition to an ICS plus another drug used for maintenance therapy [9,10]. This means that the VOYAGE study's subpopulation of interest for the benefit assessment only includes children on maintenance therapy with high-dose ICS and another controller medication (LABA and/or LTRA, see Table 7). This results in a subpopulation of 286 (295 – 9 with high-dose ICS monotherapy) patients, which corresponds to the target population of the present benefit assessment (referred to below as "subpopulation of interest"). This corresponds to 81.7% (286/350) of the subpopulation analysed by the company. Thus, at least 80% of the patients in the subpopulation of the VOYAGE study presented by the company fulfil the inclusion criterion regarding the population for the present benefit assessment in accordance with the therapeutic indication of dupilumab.

In its dossier, the company assumed that all patients with type 2 inflammation in the VOYAGE study correspond to the therapeutic indication (see previous section on the subpopulation presented by the company). It described in its dossier that only 9 patients in the subpopulation

it presented received monotherapy with an ICS. However, the company did not describe that the patients with medium-dose ICS and only one other controller medication in the VOYAGE study are not included in the therapeutic indication (severe asthma).

The following describes the implementation of the ACT in the subpopulation of interest.

2.3.3 Implementation of the appropriate comparator therapy in the subpopulation of interest in the VOYAGE study

The data of the VOYAGE study presented by the company are not suitable for assessing the added benefit of dupilumab in comparison with the ACT, as the various options specified by the G-BA for individual treatment escalation under consideration of the prior therapy were not implemented in the VOYAGE study.

According to the inclusion criteria, the patients in the VOYAGE study had uncontrolled asthma. This is also reflected in the patient characteristics: Patients in the subpopulation analysed by the company had 2.5 severe asthma exacerbations in the previous year, an ACQ-5-IA score of 2.2 at baseline and 2.5 inhalations of reliever medication within 24 h at baseline (information for the subpopulation presented by the company, in each case, mean across both study arms, see Appendix B of the full dossier assessment; information on patient characteristics for the subpopulation of interest is not available). The treatment used before the start of the study was therefore inadequate to achieve the treatment goal of asthma control. In this situation, the guidelines recommend treatment escalation [1,12].

In the control arm, no escalation of maintenance therapy was planned at baseline, while patients in the intervention arm received dupilumab as add-on therapy. No therapy escalation of the maintenance therapy was planned in the course of the study either, according to the protocol. Rather, during the course of the study, patients had to continue unchanged treatment with the maintenance therapy they had been receiving for ≥ 3 months and at a stable dose for ≥ 1 month prior to screening. Only after at least 2 severe asthma exacerbation events could maintenance therapy be escalated for the following patient populations:

- Patients on high-dose ICS monotherapy could receive a second controller medication, and
- patients on a combination of medium-dose ICS and another controller medication could be switched to a combination of high-dose ICS and another controller medication.

Maintenance therapy consisting of > 2 controller medications was not allowed at any time in the study. Thus, no treatment escalation of maintenance therapy was possible for the subpopulation of interest (see Section 2.3.2) with high-dose ICS already at baseline and another controller medication. Notwithstanding the requirements of the study protocol, no patient in the total study population of the VOYAGE study underwent an escalation of the existing maintenance therapy during the course of the study.

The following section explains to what extent the individual treatment options of the ACT would have been an escalation option in the control arm for the subpopulation of interest of patients with severe, uncontrolled asthma with type 2 inflammation, and high-dose ICS and another controller medication.

Escalation options in accordance with the ACT specified by the G-BA

The G-BA specified individual treatment escalation under consideration of the prior therapy choosing from:

- high-dose ICS and LABA and possibly LAMA

  or

- high-dose ICS and LABA and possibly LAMA and omalizumab.

According to the G-BA, the stepwise approach to drug therapy of the NVL for Asthma [1] must be taken into account. It is assumed that, in the therapeutic indication, the patients are represented in steps 5 to 6 of the stepwise approach to drug therapy for children and adolescents. Unchanged continuation of inadequate treatment of severe asthma does not comply with an ACT in severe uncontrolled asthma if the option for treatment escalation is still available.

Step 5 of the NVL for Asthma stepwise approach to drug therapy for children and adolescents includes the triple combination of high-dose ICS + LABA + LAMA or ICS + LABA + LTRA or the quadruple combination of ICS + LABA + LTRA + LAMA as escalation options for patients with existing therapy with high-dose ICS + LABA or high-dose ICS + LTRA (corresponding to the maintenance therapy at baseline in the subpopulation of interest in the VOYAGE study) [1]. These options for escalation are covered by the ACT of the G-BA ("high-dose ICS and LABA and possibly LAMA" including note on montelukast [LTRA], see Table 4).

Furthermore, according to step 6 of the stepwise approach to drug therapy of the NVL for Asthma, antibody therapy and, in justified cases, oral corticosteroids are a possible escalation in addition to step 5. However, before escalating to step 6, the effectiveness of the various therapy options of step 5 should first be evaluated [1]. Subsequently, in accordance with the ACT and the NVL for Asthma, omalizumab is an option for escalation in addition to step 5 ("high-dose ICS and LABA and possibly LAMA and omalizumab", see Table 4).

In the subpopulation of interest in the VOYAGE study, no therapy escalation was permitted in the control arm according to the study protocol, although the following options in accordance with the ACT would still have been possible for this subpopulation.

Possible escalation options for the subpopulation of interest in the VOYAGE study

3rd and 4th controller medication (LABA, LTRA and LAMA)

Escalation with a 3rd or 4th controller medication is indicated in case of inadequate asthma control under maintenance therapy with 2 controller medications according to step 5 of the NVL for Asthma. It can be assumed that all patients in the subpopulation of interest in the VOYAGE study with inadequate asthma control would have been candidates for escalation with a 3rd or 4th controller medication (LABA, LTRA and/or LAMA).

The company described in the dossier that, according to the study protocol, the addition of a 3rd asthma medication was excluded and thus the therapy with a triple combination of ICS + LABA + LAMA was not possible. The company did not address the possible triple combination of high-dose ICS + LABA + LTRA and quadruple combination of high-dose ICS + LABA + LTRA + LAMA as escalation in accordance with step 5 of the NVL for Asthma. According to the company, the fact that no LAMA was used in any patient suggests that the investigators did not consider LAMAs to be a suitable option for the children. Since LAMAs only have bronchodilator effects and thus cannot influence the pathophysiology of asthma, it is uncertain to what extent children with severe asthma benefit from adding LAMAs, the company added. This reasoning is not comprehensible, as the therapy of ICS + LAMA, which was only allowed as a dual combination in the study, is not recommended at all in the NVL for Asthma.

Additional escalation with omalizumab

According to the ACT specified by the G-BA, administration of omalizumab is another possibility of treatment escalation in IgE-mediated asthma if the criteria of the approval [13,14] and the treatment notes [15] are fully met. The SPC and the treatment notes specify various criteria, such as frequent symptoms during the day, nocturnal awakening and severe asthma exacerbations documented several times despite daily therapy with high-dose ICS and a LABA.

In the VOYAGE study, omalizumab was not allowed within 130 days prior to screening and during the entire course of the study. It is not clear from the study documents whether the patients in the VOYAGE study had ever received omalizumab before the start of the study. However, it can be assumed that the patients had not yet been treated with omalizumab.

The company determined the proportion of patients who are eligible for omalizumab, stating that it applied the criteria of the G-BA's treatment note. For this purpose, the company determined the number of patients with a total IgE level of 200 to 1300 international units (IU)/mL and an allergen-specific IgE level of ≥ 0.35 IU/mL for at least one allergen. In addition, only patients who were receiving baseline therapy with high-dose ICS and another asthma medication and had experienced severe asthma exacerbation events in the previous 12 months were included. Using the current classification for high-dose ICS according to the NVL for Asthma, the company calculated that 31.1% of the population it used would be eligible for omalizumab (15.4% using the no longer current classification for high-dose ICS according to the 2015 GINA guideline). The company concluded that, taking into account the dosage

categories according to the 2015 GINA guideline, which it considered relevant for the study, more than 80% of the patients in the population it used would not be eligible for the use of omalizumab and that the unavailability of omalizumab in the VOYAGE study therefore has a negligible influence on the informative value of the results.

Contrary to the assessment of the company, the current classification of the NVL for Asthma is considered relevant for the calculation of patients with high-dose ICS (prescription criterion according to the treatment note) and is applied to the patients in the control arm. According to the calculations of the company in Appendix 4 G of the dossier, this classification results in a proportion of 28.9% in the control arm of the population used by the company that would be eligible for omalizumab. Data for the subpopulation of interest in the VOYAGE study, which corresponds to the target population of the present benefit assessment, are not available.

Based on the calculations of the company, it is assumed overall that a relevant number of patients in the control arm would have been eligible for omalizumab as an escalation option according to step 6 of the NVL for Asthma, after the therapy options of step 5 described above had been exhausted.

Conclusion

In the VOYAGE study, the inadequate therapy was continued unchanged in the control arm at baseline and during the course of the study, although further options for therapy escalation existed. The therapy used in the control arm of the study therefore does not correspond to the current recommendations for therapy escalation in the clinical practice guidelines for asthma [1,12] and therefore also does not correspond to the ACT specified by the G-BA. The ACT of individual treatment escalation was thus not implemented in the VOYAGE study.

2.4 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of dupilumab in comparison with the ACT in children 6 to 11 years old with severe asthma with type 2 inflammation who are inadequately controlled with medium- to high-dose ICS plus another medicinal product for maintenance treatment. This results in no hint of added benefit of dupilumab in comparison with the ACT; an added benefit for these patients is therefore not proven.

2.5 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 8.

Table 8: Dupilumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Children between 6 and 11 years of age with severe asthma with type 2 inflammation[b] which is not properly controlled despite moderate-to-high-dose ICS plus one further drug as maintenance treatment[c]	Individual treatment escalation[d, e] under consideration of the prior therapy choosing from: ▪ high-dose ICS and LABA and possibly LAMA or ▪ high-dose ICS and LABA and possibly LAMA and omalizumab[f]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Characterized by raised blood eosinophils and/or raised FeNO.
c. In view of the wording of the therapeutic indication (severe asthma), it is assumed in accordance with the G-BA that therapy with dupilumab is only indicated in addition to high-dose ICS and at least one other drug for maintenance treatment or in addition to medium-dose ICS and montelukast and LABA and LAMA.
d. According to the G-BA, the stepwise approach to drug therapy of the 2020 NVL for Asthma, 4th edition [1] must be taken into account. It is assumed that, in the therapeutic indication, the patients are represented in steps 5 to 6 of the stepwise approach to drug therapy for children and adolescents. Montelukast is only approved as additional treatment in patients suffering from mild to moderate persistent asthma. Nevertheless, patients with severe asthma who receive montelukast in compliance with the recommendation of the 2020 NVL for Asthma in the present therapeutic indication can be included in the population relevant to the benefit assessment.
e. Unchanged continuation of inadequate treatment of severe asthma does not comply with an ACT in severe uncontrolled asthma if the option for treatment escalation is still available.
f. If the criteria required for the use of omalizumab are met.

FeNO: fraction of exhaled nitric oxide; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; NVL: National Care Guideline

The assessment described above deviates from that of the company, which derived a hint of a major added benefit on the basis of the data of the VOYAGE study it provided in Module 4 F.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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

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