Dupilumab (COPD)

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

EXTRACT

Project: A24-79 Version: 1.0 Status: 28 Oct 2024 DOI: 10.60584/A24-79_en

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Dupilumab (COPD) – 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.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Dupilumab (COPD) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

31 July 2024

Internal Project No.

A24-79

DOI-URL

https://doi.org/10.60584/A24-79_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Martin Edelmann, Lungenpraxis Aalen, Aalen, Germany

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

Patient and family involvement

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

IQWiG employees involved in the dossier assessment

- Sascha Abbas
- Tobias Effertz
- Simone Heß
- Michaela Florina Kerekes
- Jona Lilienthal
- Daniela Preukschat
- Min Ripoll
- Claudia Selbach

Keywords

Dupilumab, Pulmonary Disease – Chronic Obstructive, Benefit Assessment, NCT03930732, NCT04456673

Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
COPD	chronic obstructive pulmonary disease
EPAR	European Public Assessment Report
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GINA	Global Initiative for Asthma
ICS	inhaled corticosteroid
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LABA	long-acting beta-2 agonist
LAMA	long-acting muscarinic antagonist
MRC	Medical Research Council
NYHA	New York Heart Association
PDE4	phosphodiesterase type 4
post-BD	post-bronchodilator
RCT	randomized controlled trial
SABA	short-acting beta-2 agonist
SAE	serious adverse event
SAMA	short-acting muscarinic antagonist
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

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 31 July 2024.

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 adult patients with uncontrolled chronic obstructive pulmonary disease (COPD) characterized by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta-2 agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate.

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]
Add-on maintenance treatment of adult patients with uncontrolled COPD characterized by raised blood eosinophils on a combination of an ICS, a LABA, and a LAMA, or on a combination of a LABA and a LAMA if ICS is not appropriate[b, c]	LABA and LAMA and, if applicable, ICS and roflumilast[d] if the criteria necessary for the use of roflumilast are met[c, e, f]

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the patient population also includes patients who are already receiving a triple therapy of LAMA + LABA + ICS or a dual therapy of LAMA + LABA, if ICS is contraindicated, and who do not fulfil the criteria for the additional use of roflumilast.
c. Measures that particularly affect the symptom of frequent exacerbation, such as acetylcysteine administration and saline inhalations, should be carried out in both arms of the study.
d. Roflumilast can be used as an ACT option only in patients who completely fulfil the criteria of the approval. According to the SPC, treatment with roflumilast is indicated for maintenance treatment of severe COPD (FEV1 post-bronchodilator < 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add-on to bronchodilator treatment.
e. Unchanged continuation of inadequate treatment of COPD does not comply with an ACT if the option for treatment escalation is still available.
f. In order to increase the interpretability of the results, the G-BA recommends documenting the background medication (LABA, LAMA and, if applicable, ICS) with dosage and duration during the study and presenting it in the dossier.

ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; SPC: Summary of Product Characteristics

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 were used for the derivation of added benefit.

Results

The check of the completeness of the study pool identified the RCTs BOREAS and NOTUS on the direct comparison of dupilumab versus the ACT, for which it is unclear (based on the available information) whether they contain a subpopulation relevant for the present benefit assessment. The company used a subpopulation of each of these studies for the assessment of the added benefit of dupilumab.

Evidence provided by the company

BOREAS and NOTUS are double-blind RCTs on the comparison of dupilumab with placebo. They included adult patients aged ≥ 40 to ≤ 80 years (BOREAS) or ≥ 40 to ≤ 85 years (NOTUS) with moderate to severe COPD (post-bronchodilator [post-BD] forced expiratory volume in 1 second [FEV1]/forced vital capacity [FVC] ratio < 0.70, post-BD FEV1 of > 30% to ≤ 70% predicted; Medical Research Council [MRC] Dyspnoea Scale grade ≥ 2). Patients with a current diagnosis of asthma or any history of asthma and patients with New York Heart Association (NYHA) class III or IV were excluded from both studies. Patients had to have a high exacerbation risk defined as exacerbation history of ≥ 2 moderate or ≥ 1 severe exacerbations within 1 year prior to study start. At least one exacerbation must have occurred during treatment with an ICS (if indicated), LAMA and LABA. Patients with exacerbations within 4 weeks prior to or during the screening period were excluded from both studies. Patients had to have an elevation in blood eosinophils, defined as ≥ 300 cells/µL, at least once during the screening period. In addition, the study populations were restricted to current or former smokers with ≥ 10 pack years and to patients with signs and symptoms of chronic bronchitis (chronic productive cough) for 3 months in the year up to study start.

In the BOREAS study, a total of 939 patients were randomly allocated in a 1:1 ratio to treatment with dupilumab (N = 468) or placebo (N = 471). In the NOTUS study, 935 patients were randomly allocated in a 1:1 ratio to treatment with dupilumab (N = 470) or placebo (N = 465). In the BOREAS study, randomization was stratified by country and high-dose ICS (yes, no), in the NOTUS study additionally by smoking status (current: yes, no).

Treatment with dupilumab was in compliance with the dosing specifications of the Summary of Product Characteristics (SPC). Patients in both study arms of both the BOREAS and the NOTUS study had to have received maintenance therapy consisting of LABA + LAMA + ICS – LABA + LAMA allowed if ICS was contraindicated – for 3 months prior to randomization, and with a stable dose of medication for ≥ 1 month prior to screening. This therapy had to be continued unchanged at a stable dosage during the studies. Dose adjustment of maintenance

therapy was allowed after 1 severe or 2 moderate COPD exacerbations. Notwithstanding this, systemic corticosteroids up to a maximum of 6 weeks were permitted for the treatment of exacerbations, as well as short-acting beta-2 agonists (SABAs) and short-acting muscarinic antagonists (SAMAs) as rescue medication.

Both studies include a screening period of up to 4 weeks, a 52-week treatment phase and a 12-week follow-up phase. The primary outcome of both studies was the annualized rate of moderate or severe COPD exacerbations. Secondary outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Subpopulation of BOREAS and NOTUS presented by the company

In the BOREAS and NOTUS studies presented by the company, almost all patients received a triple therapy consisting of LABA + LAMA + ICS. The new use of phosphodiesterase type 4 (PDE4) inhibitors such as roflumilast – as a treatment component in accordance with the ACT – was not permitted at the start of the study or during the study in either study. According to the inclusion criteria, these drugs were only permitted if they had already been used as stable treatment > 6 months prior to screening. This only affected 11 patients (1.2%) in the BOREAS study and 7 patients (0.7%) in the NOTUS study. According to the SPC, roflumilast is indicated for severe COPD with a post-BD FEV1 < 50% predicted. In its dossier, the company therefore formed subpopulations of BOREAS and NOTUS, each of which only included patients with a baseline post-BD FEV1 ≥ 50% predicted, as this subpopulation did not meet the criteria for the use of roflumilast. In the presented subpopulation of the 2 studies, the company assumed the ACT to be implemented for patients who are not eligible for treatment with roflumilast, and derived proof of considerable added benefit on the basis of a meta-analysis of the subpopulations of both studies.

Assessment of the evidence presented by the company

Implementation of the appropriate comparator therapy

Since no treatment escalation with roflumilast was permitted in BOREAS and NOTUS, the company's restriction of the total population of BOREAS and NOTUS to patients with a post-BD FEV1 ≥ 50% predicted to form a subpopulation who are not eligible for treatment with roflumilast is comprehensible. Nevertheless, it is unclear whether escalation options in the sense of the ACT still existed at baseline and during the studies. In its notes on the ACT, the G-BA therefore recommended documenting the background medication (LABA and LAMA and, if applicable, ICS) with dosage and duration during the study and presenting it in the dossier in order to increase the interpretability of the results. Different drugs and drug combinations of ICS, LABA and LAMA (partly single agents and partly combination preparations) were used in BOREAS and NOTUS. In the subpopulation presented by the company, ICS was mainly used as a combination preparation in the BOREAS study, and almost exclusively as a single agent in the NOTUS study. For ICS in particular, the SPC differs in terms

of dosage specifications and escalation options depending on the drug or drug combination. No information on the respective dosages of the preparations used is available for either study. The assessment of study relevance or relevance of a subpopulation of BOREAS and NOTUS for the present research question requires comprehensive information on the dosages of the background medication, in particular for ICS, for the respective drugs or drug combinations used. Based on the available data, it is neither shown that dosing was in compliance with the approval nor that treatment escalation options, e.g. in terms of an ICS dose increase, had been exhausted at study start. If escalation options were still available, adjustments were only possible during the studies and only with notable restrictions (after 2 moderate or 1 severe exacerbation).

Definition of patients with raised blood eosinophils in COPD

According to the SPC, dupilumab is approved for adult patients with COPD characterized by raised blood eosinophils. The SPC does not provide any information on the threshold value for raised blood eosinophils, and only refers to Section 5.1, where BOREAS and NOTUS are described. BOREAS and NOTUS included patients with a blood eosinophil count of ≥ 300 cells/µL at screening. Up to 3 measurements were allowed to fulfil the inclusion criterion. At baseline, the proportion of patients with ≥ 300 cells/µL in the subpopulation presented by the company was only 63% each in BOREAS and NOTUS . Thus, based on the threshold value of 300 cells/µL, there was already a relevant proportion of patients without raised blood eosinophils at baseline in BOREAS and NOTUS. There is currently no clear definition of COPD characterized by raised blood eosinophils. It is therefore unclear whether the procedure defined in BOREAS and NOTUS for determining raised blood eosinophils (a single elevation of ≥ 300 cells/µL at screening was sufficient [with up to 3 measurements] and measurement at baseline was not taken into account) is adequate.

Summary

In summary, the assessment of study relevance or relevance of a subpopulation of BOREAS and NOTUS for the present research question requires comprehensive information on the dosages of the background medication, in particular for ICS, for the respective drugs or drug combinations used. In its notes on the ACT and in the consultation, the G-BA also requested documenting the background medication with dosage and duration during the study, and presenting it in the dossier. The patient group relevant for the present research question comprises patients whose therapies were dosed sufficiently in compliance with the approval and for whom therapy escalation options (e.g. in the sense of an ICS dose increase) had been exhausted at the start of the study. It is unclear whether this patient group was included in BOREAS and NOTUS. In addition, the procedure defined in BOREAS and NOTUS for determining raised blood eosinophils should be discussed.

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.

Table 3: Dupilumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Add-on maintenance treatment of adult patients with uncontrolled COPD characterized by raised blood eosinophils on a combination of an ICS, a LABA, and a LAMA, or on a combination of a LABA and a LAMA if ICS is not appropriate[b, c]	LABA and LAMA and, if applicable, ICS and roflumilast[d] if the criteria necessary for the use of roflumilast are met[c, e, f]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the patient population also includes patients who are already receiving a triple therapy of LAMA + LABA + ICS or a dual therapy of LAMA + LABA, if ICS is contraindicated, and who do not fulfil the criteria for the additional use of roflumilast.
c. Measures that particularly affect the symptom of frequent exacerbation, such as acetylcysteine administration and saline inhalations, should be carried out in both arms of the study.
d. Roflumilast can be used as an ACT option only in patients who completely fulfil the criteria of the approval. According to the SPC, treatment with roflumilast is indicated for maintenance treatment of severe COPD (FEV1 post-bronchodilator < 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add-on to bronchodilator treatment.
e. Unchanged continuation of inadequate treatment of COPD does not comply with an ACT if the option for treatment escalation is still available.
f. In order to increase the interpretability of the results, the G-BA recommends documenting the background medication (LABA, LAMA and, if applicable, ICS) with dosage and duration during the study and presenting it in the dossier.

ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; SPC: Summary of Product Characteristics

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 [1,2].

I 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 adult patients with uncontrolled COPD characterized by raised blood eosinophils on a combination of an ICS, a LABA, and a LAMA, or on a combination of a LABA and a LAMA if ICS is not appropriate.

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]
Add-on maintenance treatment of adult patients with uncontrolled COPD characterized by raised blood eosinophils on a combination of an ICS, a LABA, and a LAMA, or on a combination of a LABA and a LAMA if ICS is not appropriate[b, c]	LABA and LAMA and, if applicable, ICS and roflumilast[d] if the criteria necessary for the use of roflumilast are met[c, e, f]

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the patient population also includes patients who are already receiving a triple therapy of LAMA + LABA + ICS or a dual therapy of LAMA + LABA, if ICS is contraindicated, and who do not fulfil the criteria for the additional use of roflumilast.
c. Measures that particularly affect the symptom of frequent exacerbation, such as acetylcysteine administration and saline inhalations, should be carried out in both arms of the study.
d. Roflumilast can be used as an ACT option only in patients who completely fulfil the criteria of the approval. According to the SPC, treatment with roflumilast is indicated for maintenance treatment of severe COPD (FEV1 post-BD < 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add-on to bronchodilator treatment [3].
e. Unchanged continuation of inadequate treatment of COPD does not comply with an ACT if the option for treatment escalation is still available.
f. In order to increase the interpretability of the results, the G-BA recommends documenting the background medication (LABA, LAMA and, if applicable, ICS) with dosage and duration during the study and presenting it in the dossier.

ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; SPC: Summary of Product Characteristics

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 were used for the derivation of 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: 1 July 2024)
- bibliographical literature search on dupilumab (last search on 1 July 2024)
- search in trial registries/trial results databases for studies on dupilumab (last search on 1 July 2024)
- search on the G-BA website for dupilumab (last search on 1 July 2024)

To check the completeness of the study pool:

- search in trial registries for studies on dupilumab (last search on 16 August 2024); for search strategies, see I Appendix A of the full dossier assessment

The check identified the RCTs BOREAS [4-7] and NOTUS [8-11] on the direct comparison of dupilumab versus the ACT, for which it is unclear (based on the available information) whether they contain a subpopulation relevant for the present benefit assessment. The company used a subpopulation of each of these studies for the assessment of the added benefit of dupilumab.

The data presented by the company are unsuitable for assessing any added benefit of dupilumab in comparison with the ACT. First, BOREAS and NOTUS are described below. Subsequently, the subpopulations of BOREAS and NOTUS presented by the company are characterized and reasons are given as to why the data presented are not suitable for assessing the added benefit of dupilumab in comparison with the ACT.

I 3.1 Data presented by the company

BOREAS and NOTUS

Table 5 and Table 6 describe the BOREAS and NOTUS studies presented by the company for the benefit assessment.

Table 5: Characteristics of the studies included by the company – RCT, direct comparison: dupilumab vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
BOREAS	RCT, double-blind, parallel	Adults (≥ 40 to ≤ 80 years) with moderate to severe COPD[b] ▪ high exacerbation risk defined as exacerbation history of ≥ 2 moderate or ≥ 1 severe exacerbations within 1 year prior to study start[c, d] ▪ blood eosinophils ≥ 300/µL at screening ▪ signs and symptoms of chronic bronchitis (chronic productive cough) for 3 months in the year up to study start ▪ current or former smokers with ≥ 10 pack years	Dupilumab (N = 468) Placebo (N = 471) Subpopulation thereof analysed by the company[e]: dupilumab (n = 241) placebo (n = 231)	Screening: up to 4 weeks Treatment: 52 weeks Observation: 12 weeks	275 centres: Argentina, Bulgaria, Canada, Chile, China, Czech Republic, Denmark, Finland, Germany, Hungary, Israel, Italy, Japan, Mexico, Poland, Romania, Russia, Slovakia, South Korea, Spain, Sweden, Turkey, Ukraine, and United States 5/2019–5/2023 Data cut-offs: ▪ 8 February 2023: final analysis[f] ▪ 2 May 2023: addendum[f]	Primary: annualized rate of moderate or severe COPD exacerbations Secondary: morbidity, health-related quality of life, AEs

Table 5: Characteristics of the studies included by the company – RCT, direct comparison: dupilumab vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
NOTUS	RCT, double-blind, parallel	See BOREAS study, except for the following difference: ▪ inclusion of patients ≥ 40 to < 85 years	Dupilumab (N = 470) Placebo (N = 465) Thereof subpopulation analysed by the company[e]: dupilumab (n = 217) placebo (n = 236)	See BOREAS study	329 centres: Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Czech Republic, France, Germany, Greece, Hungary, Latvia, Lithuania, Mexico, Netherlands, Peru, Poland, Portugal, Romania, Russia, Serbia, Slovakia, South Africa, Spain, Ukraine, United Kingdom, and United States 7/2020–5/2024 Data cut-offs: ▪ Interim analysis: 29 September 2023[g] ▪ Final analysis: Results are not yet available	See BOREAS study

Table 5: Characteristics of the studies included by the company – RCT, direct comparison: dupilumab vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes comprise exclusively data based on the information provided by the company's Module 4. b. Post-BD FEV1/FVC < 0.70, post-BD FEV1 of > 30% to ≤ 70% predicted; MRC Dyspnoea Scale grade ≥ 2; current diagnosis of asthma or any history of asthma excluded. c. At least one exacerbation must have occurred during treatment with an ICS (if indicated), LAMA and LABA; moderate: exacerbation requiring either systemic corticosteroids and/or antibiotics, with one of the 2 required moderate exacerbations requiring the use of systemic corticosteroids; severe: exacerbation requiring hospitalization or observation for > 24 hours in an emergency department/urgent care facility. d. Patients with exacerbations within 4 weeks prior to or during the screening period were excluded from the study. e. Patients with post-BD FEV1 ≥ 50%. f. The final analysis was carried out after all patients had reached 52 weeks of treatment. At this time, some patients were still in the 12-week follow-up observation period. The addendum contains additional data after the final analysis. g. Protocol amendment 3 of 28 October 2023 introduced an interim analysis (database lock: 1 November 2023) to potentially show efficacy for the primary outcome before all patients had reached 52 weeks of treatment. According to the company, the introduction of an interim analysis was based on the results of the BOREAS study and in consultation with a regulatory authority. At that time, not all patients had yet reached 52 weeks of treatment. AE: adverse event; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; MRC: Medical Research Council; n: number of analysed patients; N: number of randomized patients; post-BD: post-bronchodilator; RCT: randomized controlled trial					

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

Study	Intervention	Comparison
BOREAS	Dupilumab 300 mg SC, every 2 weeks	Placebo SC every 2 weeks
	▪ No dose adjustments planned	
	Required pretreatment ▪ triple therapy (LABA + LAMA + ICS) for 3 months prior to randomization with a stable dose for ≥ 1 month prior to screening (LABA + LAMA allowed if ICS contraindicated) **Disallowed pretreatment** ▪ treatment with oxygen > 12 hours/day ▪ anti-immunoglobulin E (omalizumab) within 130 days, or any other biologic therapy or immunosuppressant to treat inflammatory disease or autoimmune disease as well as other diseases within 2 months or 5 half-lives prior to screening ▪ macrolide antibiotics (e.g. azithromycin), unless stable therapy for > 12 months **Maintenance treatment during the study** ▪ continuation of the triple therapy regimen administered at the start of the study (or LABA + LAMA if ICS is contraindicated) at a stable dosage[a] **Allowed concomitant treatment** ▪ systemic corticosteroids up to a maximum of 6 weeks for the treatment of exacerbations ▪ rescue medication with SABA or SAMA **Disallowed concomitant treatment** ▪ any biologic agent within 5 half-lives before study start and during the course of the study ▪ PDE4 inhibitors (roflumilast) and theophylline, unless stable > 6 months prior to screening ▪ new chronic use of macrolide antibiotics (e.g. azithromycin) (except for the treatment of exacerbations) ▪ systemic immunosuppressants including chronic use of systemic corticosteroids ▪ IV immunoglobulins ▪ beta-blockers (except for a selective beta-1 blocker used with dose stable for 1 month prior to screening)	
NOTUS	Dupilumab 300 mg SC, every 2 weeks	Placebo SC every 2 weeks
	▪ No dose adjustments planned	
	Pretreatment and concomitant treatment See BOREAS study, except for the following difference: **Disallowed pretreatment** ▪ long-term treatment with oxygen > 4.0 L/min, or if a patient requires more than 2.0 L/min in order to maintain oxygen saturation > 88%[b]	

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

Study	Intervention	Comparison
a. Patients had to be willing not to adjust their maintenance therapy during the study. After successful management of an acute exacerbation (e.g. with oral corticosteroids and/or antibiotics), all efforts had to be made to resume the initial maintenance treatment regimen if in the investigator's opinion this was medically acceptable. Dose adjustment of maintenance therapy was allowed after 1 severe or 2 moderate COPD exacerbations. b. With Protocol Amendment 2 of 16 December 2021, the original exclusion criterion of treatment with oxygen of > 12 hours/day was revised to also include patients with long-term oxygen therapy under the conditions described. COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; IV: intravenous; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; PDE4: phosphodiesterase type 4; RCT: randomized controlled trial; SABA: short-acting beta-2 agonist; SAMA: short-acting muscarinic antagonist; SC: subcutaneous		

BOREAS and NOTUS are double-blind RCTs on the comparison of dupilumab with placebo. They included adult patients aged ≥ 40 to ≤ 80 years (BOREAS) or ≥ 40 to ≤ 85 years (NOTUS) with moderate to severe COPD (post-BD FEV1/FVC ratio < 0.70, post-BD FEV1 of > 30% to ≤ 70% predicted; MRC Dyspnoea Scale grade ≥ 2). Patients with a current diagnosis of asthma or any history of asthma and patients with NYHA class III or IV were excluded from both studies. Patients had to have a high exacerbation risk defined as exacerbation history of ≥ 2 moderate or ≥ 1 severe exacerbations within 1 year prior to study start. At least one exacerbation must have occurred during treatment with an ICS (if indicated), LAMA and LABA. Patients with exacerbations within 4 weeks prior to or during the screening period were excluded from both studies. Patients had to have an elevation in blood eosinophils, defined as ≥ 300 cells/µL, at least once during the screening period. In addition, the study populations were restricted to current or former smokers with ≥ 10 pack years and to patients with signs and symptoms of chronic bronchitis (chronic productive cough) for 3 months in the year up to study start.

In the BOREAS study, a total of 939 patients were randomly allocated in a 1:1 ratio to treatment with dupilumab (N = 468) or placebo (N = 471). In the NOTUS study, 935 patients were randomly allocated in a 1:1 ratio to treatment with dupilumab (N = 470) or placebo (N = 465). In the BOREAS study, randomization was stratified by country and high-dose ICS (yes, no), in the NOTUS study additionally by smoking status (current: yes, no).

Treatment with dupilumab was in compliance with the dosing specifications of the SPC [12]. Patients in both study arms of both the BOREAS and the NOTUS study had to have received maintenance therapy consisting of LABA + LAMA + ICS – LABA + LAMA allowed if ICS was contraindicated – for 3 months prior to randomization, and with a stable dose of medication for ≥ 1 month prior to screening. This therapy had to be continued unchanged at a stable

dosage during the studies. Dose adjustment of maintenance therapy was allowed after 1 severe or 2 moderate COPD exacerbations. Notwithstanding this, systemic corticosteroids up to a maximum of 6 weeks were permitted for the treatment of exacerbations, as well as SABAs and SAMAs as rescue medication.

Both studies include a screening period of up to 4 weeks, a 52-week treatment phase and a 12-week follow-up phase. The primary outcome of both studies was the annualized rate of moderate or severe COPD exacerbations. Secondary outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Subpopulation of BOREAS and NOTUS presented by the company

In the BOREAS and NOTUS studies presented by the company, almost all patients received a triple therapy consisting of LABA + LAMA + ICS. Only 20 patients in the BOREAS study (2.1%) and 10 patients in the NOTUS study (1.1%) received LABA + LAMA without ICS. The new use of PDE4 inhibitors such as roflumilast – as a treatment component in accordance with the ACT – was not permitted at the start of the study or during the study in either study. According to the inclusion criteria, these drugs were only permitted if they had already been used as stable treatment > 6 months prior to screening. This only affected 11 patients (1.2%) in the BOREAS study and 7 patients (0.7%) in the NOTUS study. According to the SPC, roflumilast is indicated for severe COPD with a post-BD FEV1 < 50% predicted [3]. In its dossier, the company therefore formed subpopulations of BOREAS and NOTUS, each of which only included patients with a baseline post-BD FEV1 ≥ 50% predicted, as this subpopulation did not meet the criteria for the use of roflumilast. In the presented subpopulation of the 2 studies, the company assumed the ACT to be implemented for patients who are not eligible for treatment with roflumilast, and derived proof of considerable added benefit on the basis of a meta-analysis of the subpopulations of both studies.

I 3.2 Assessment of the data presented by the company

The data presented by the company are unsuitable for assessing the benefit of dupilumab in comparison with the ACT. This is explained below.

Implementation of the appropriate comparator therapy

According to the inclusion criteria, patients in BOREAS and NOTUS had inadequately controlled COPD. Patients had to have a history of ≥ 1 severe or ≥ 2 moderate exacerbations within 1 year prior to study start. In this situation, the guideline recommends treatment escalation [13]. However, unchanged continuation of inadequate treatment of COPD does not comply with the ACT if the option for treatment escalation is still available. In BOREAS and NOTUS, patients in the intervention arm received dupilumab, whereas patients in the comparator arm received placebo. Thus, the medication in the comparator arm given at baseline was continued unchanged in the studies. Patients had to be willing not to adjust their

maintenance therapy during the study. After successful management of an acute exacerbation (e.g. with oral corticosteroids and/or antibiotics), all efforts had to be made to resume the initial maintenance treatment regimen if in the investigator's opinion this was medically acceptable. Dose adjustment of maintenance therapy was allowed only after 1 severe or 2 moderate COPD exacerbations.

The following text explains to what extent there were still possibilities for escalation at baseline in the subpopulation of BOREAS and NOTUS presented by the company, and whether this could be examined on the basis of the data presented by the company.

Treatment escalation with Roflumilast

According to the guideline, in patients who are already receiving triple therapy consisting of LABA + LAMA + ICS, escalation with roflumilast is an option for patients who fulfil the criteria for the use of roflumilast [13]. Accordingly, roflumilast is part of the ACT, provided the necessary criteria for its use are met. Since no treatment escalation with roflumilast was permitted in BOREAS and NOTUS, the company's restriction of the total population of BOREAS and NOTUS to patients with a post-BD FEV1 ≥ 50% predicted to form a subpopulation who are not eligible for treatment with roflumilast (see previous section) is comprehensible. Roflumilast is approved for severe COPD (FEV1 post-BD < 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add-on to bronchodilator treatment [3]. It can therefore be assumed that, based on the inclusion criteria of BOREAS and NOTUS (exacerbations and symptoms of chronic bronchitis in the year before study start), roflumilast would have been a possible escalation option in the population with post-BD FEV1 < 50%, which was not used by the company. Nevertheless, there is still some uncertainty as to whether the subpopulation used by the company includes patients for whom roflumilast was not an option at baseline but would have been an option during the study.

Treatment escalation as part of dose increases

Despite the restriction to patients who were not eligible for roflumilast at baseline, it is unclear whether the subpopulations of BOREAS and NOTUS presented by the company still had escalation options in the sense of the ACT at baseline and during the studies. In its notes on the ACT and in the consultation [14], the G-BA therefore recommended documenting the background medication (LABA and LAMA and, if applicable, ICS) with dosage and duration during the study and presenting it in the dossier in order to increase the interpretability of the results.

Different drugs and drug combinations of ICS, LABA and LAMA (partly single agents and partly combination preparations) were used in BOREAS and NOTUS. The company presented corresponding information in Module 4 G of its dossier. In the subpopulation presented by the company, ICS was mainly used as a combination preparation in the BOREAS study (drug

combinations in > 10% of patients: fluticasone propionate/salmeterol xinafoate, budesonide/formoterol fumarate [23.9% each] and fluticasone furoate/umeclidinium bromide/vilanterol trifenatate [11.9%]), and almost exclusively as a single agent in the NOTUS study (drugs in > 10% of patients: fluticasone propionate [25.6%], budesonide and fluticasone furoate [23.6% each], beclometasone dipropionate [16.8%]). For ICS in particular, the SPC differs in terms of dosage specifications and escalation options depending on the drug or drug combination. No information on the respective dosages of the preparations used is available for either study. Thus, no data are available that show that the respective drugs were administered in compliance with the SPCs. In addition, no data are available to show that there were no more options for escalating treatment at baseline or during the study in terms of increasing the dose.

In its dossier, the company presented the ICS dose only as fluticasone propionate equivalent. According to this information, the median ICS dose in the subpopulations presented by the company was 500 µg in fluticasone propionate equivalents (see I Appendix B, Table 9, of the full dossier assessment). In addition, the company used the characteristic of high ICS dose (yes/no), using the drug-specific threshold values according to the 2014 Global Initiative for Asthma (GINA) Guideline [15]. Based on this categorization, in the subpopulation presented, 22.5% of patients in the comparator arm of the BOREAS study and 28.4% of patients in the comparator arm of the NOTUS study received high-dose ICS (see I Appendix B, Table 9 of the full dossier assessment).

The low proportion of patients with high-dose ICS suggests that baseline dosing of patients was potentially too low or not in compliance with the SPC. For example, the drug fluticasone propionate frequently used in the BOREAS study (31.1% [n = 147] in the subpopulation of the company) is used in a dose of 1000 µg/day for COPD according to the SPC, which corresponds to the maximum dose for asthma [16,17]. According to the company's categorization, these 147 patients should all fall into the group of patients with high-dose ICS (> 500 µg fluticasone propionate/day) [15]. In the BOREAS study, however, only 25.2% (n = 119) of patients in the subpopulation were treated with high-dose ICS.

In summary, the assessment of study relevance or relevance of a subpopulation of BOREAS and NOTUS for the present research question requires comprehensive information on the dosages of the background medication, in particular for ICS, for the respective drugs or drug combinations used. Based on the available data, it is neither shown that dosing was in compliance with the approval nor that treatment escalation options, e.g. in terms of an ICS dose increase, had been exhausted at study start. If escalation options were still available, adjustments were only possible during the studies and only with notable restrictions (after 2 moderate or 1 severe exacerbation). In the overall population of BOREAS and NOTUS, the

adjustment of the concomitant medication (number and/or dose) was only carried out in 13 and 9 exacerbations respectively (see I Appendix B, Table 10, of the full dossier assessment).

Since, in addition to treatment escalations, de-escalations (e.g. reduction in ICS dose due to side effects, especially pneumonia) may also be necessary on a patient-specific basis, there is also uncertainty regarding the extent to which these were necessary and could not be implemented because the concomitant medication was to be continued unchanged.

Definition of patients with raised blood eosinophils in COPD

According to the SPC, dupilumab is approved for adult patients with COPD characterized by raised blood eosinophils [12]. The SPC does not provide any information on the threshold value for raised blood eosinophils, and only refers to Section 5.1, where BOREAS and NOTUS are described. BOREAS and NOTUS included patients with a blood eosinophil count of ≥ 300 cells/µL at screening (4 weeks+/- 1 week prior to randomization/baseline). Up to 3 measurements were allowed to fulfil the inclusion criterion. At baseline, the proportion of patients with ≥ 300 cells/µL in the subpopulation presented by the company was only 63% each in BOREAS and NOTUS (see I Appendix B, Table 8, of the full dossier assessment). Thus, based on the threshold value of 300 cells/µL, there was already a relevant proportion of patients without raised blood eosinophils at baseline in BOREAS and NOTUS.

According to the European Public Assessment Report (EPAR), a threshold value was deliberately not given in the therapeutic indication due to the fluctuating number of eosinophils in the blood; instead, reference was made to section 5.1 of the SPC, which contains information on the corresponding studies [18]. COPD guidelines also provide no definition of COPD characterized by raised blood eosinophils. An eosinophil count ≥ 300 cells/µL is defined as the threshold value for administering ICS [13,19], whereby patients with < 100 cells/µL may have no additional benefit from ICS administration [13].

Dupilumab is also approved for patients with severe asthma with type 2 inflammation (characterized by raised blood eosinophils and/or raised fraction of exhaled nitric oxide). In this therapeutic indication, raised blood eosinophils are based on a threshold value of ≥ 150 cells/µL [12,20]. In addition, according to the National Disease Management Guideline for Asthma, at least 2 measurements of > 300 eosinophils/µL blood (outside of exacerbations, measured at adequate intervals and without medication with systemic corticosteroids) are considered necessary for the diagnosis of severe eosinophilic asthma [20].

Based on guideline information, a threshold value of 300 cells/µL for raised blood eosinophils in COPD appears adequate. This value was also used for screening in BOREAS and NOTUS. However, a larger proportion of patients had values below this threshold at baseline. No information is available on the proportion of patients with baseline eosinophil count < 150 cells/µL or < 100 cells/µL for the subpopulations presented by the company. According

to the EPAR, the proportion of patients with < 150 cells/µL in the pooled total population of both studies was 9% [18]. It is currently unclear how meaningful it is to have at least 2 measurements, analogous to the definition for severe eosinophilic asthma, for the patient population of the present research question. According to the EPAR, the proportion of patients with ≥ 300 cells/µL in all measurements at screening and baseline was only 47% in the pooled total population of both studies (data for the subpopulation presented by the company are not available) [18]. Subgroup analyses according to baseline eosinophil count were also discussed in the EPAR. These are not available for the present benefit assessment, however.

In summary, there is currently no clear definition of COPD characterized by raised blood eosinophils. It is therefore unclear whether the procedure defined in BOREAS and NOTUS for determining raised blood eosinophils (a single elevation of ≥ 300 cells/µL at screening was sufficient [with up to 3 measurements] and measurement at baseline was not taken into account) is adequate.

Summary

In summary, the assessment of study relevance or relevance of a subpopulation of BOREAS and NOTUS for the present research question requires comprehensive information on the dosages of the background medication, in particular for ICS, for the respective drugs or drug combinations used. In its notes on the ACT and in the consultation, the G-BA also requested documenting the background medication with dosage and duration during the study, and presenting it in the dossier. The patient group relevant for the present research question comprises patients whose therapies were dosed sufficiently in compliance with the approval and for whom therapy escalation options (e.g. in the sense of an ICS dose increase) had been exhausted at the start of the study. It is unclear whether this patient group was included in BOREAS and NOTUS. In addition, the procedure defined in BOREAS and NOTUS for determining raised blood eosinophils should be discussed.

I 3.3 Results

No suitable data are available for the benefit assessment of dupilumab as add-on maintenance treatment in comparison with the ACT in adult patients with uncontrolled COPD characterized by raised blood eosinophils on a combination of an ICS, a LABA, and a LAMA, or on a combination of a LABA and a LAMA if ICS is not appropriate. There is no hint of an added benefit of dupilumab in comparison with the ACT; an added benefit is therefore not proven.

I 4 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 7.

Table 7: Dupilumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Add-on maintenance treatment of adult patients with uncontrolled COPD characterized by raised blood eosinophils on a combination of an ICS, a LABA, and a LAMA, or on a combination of a LABA and a LAMA if ICS is not appropriate[b, c]	LABA and LAMA and, if applicable, ICS and roflumilast[d] if the criteria necessary for the use of roflumilast are met[c, e, f]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the patient population also includes patients who are already receiving a triple therapy of LAMA + LABA + ICS or a dual therapy of LAMA + LABA, if ICS is contraindicated, and who do not fulfil the criteria for the additional use of roflumilast.
c. Measures that particularly affect the symptom of frequent exacerbation, such as acetylcysteine administration and saline inhalations, should be carried out in both arms of the study.
d. Roflumilast can be used as an ACT option only in patients who completely fulfil the criteria of the approval. According to the SPC, treatment with roflumilast is indicated for maintenance treatment of severe COPD (FEV1 post-BD < 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add-on to bronchodilator treatment [3].
e. Unchanged continuation of inadequate treatment of COPD does not comply with an ACT if the option for treatment escalation is still available.
f. In order to increase the interpretability of the results, the G-BA recommends documenting the background medication (LABA, LAMA and, if applicable, ICS) with dosage and duration during the study and presenting it in the dossier.

ACT: appropriate comparator therapy; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; SPC: Summary of Product Characteristics

The assessment described above departs from that by the company, which used BOREAS and NOTUS to derive proof of considerable added benefit for the subpopulation of patients who are not eligible for treatment with roflumilast. The company did not derive any added benefit for patients who are eligible for treatment with roflumilast.

The G-BA decides on the added benefit.

I 5 References for English extract

Please see full dossier assessment for full reference list.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

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

3. Elpen. Roflumilast Elpen [online]. 2022 [Accessed: 11.09.2024]. URL: https://www.fachinfo.de.

4. Sanofi-aventis Recherche & Développement. A Randomized, Double-blind, Placebo-controlled, Parallel-group, 52-week Pivotal Study to Assess the Efficacy, Safety, and Tolerability of Dupilumab in Patients with Moderate-to-severe Chronic Obstructive Pulmonary Disease (COPD) with Type 2 inflammation [online]. [Accessed: 20.08.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-001953-28.

5. Bhatt SP, Rabe KF, Hanania NA et al. Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts. N Engl J Med 2023; 389(3): 205-214. https://doi.org/10.1056/NEJMoa2303951.

6. Sanofi-Aventis. A randomized, double-blind, placebo-controlled, parallel-group, 52-week pivotal study to assess the efficacy, safety, and tolerability of dupilumab in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) with type 2 inflammation (BOREAS); study EFC15804; clinical study report [unpublished]. 2023.

7. Sanofi. Pivotal Study to Assess the Efficacy, Safety and Tolerability of Dupilumab in Patients With Moderate-to-severe COPD With Type 2 Inflammation (BOREAS) [online]. 2024 [Accessed: 20.08.2024]. URL: https://clinicaltrials.gov/study/NCT03930732.

8. Sanofi-aventis Recherche & Développement. A Randomized, Double-blind, Placebo-controlled, Parallel-group, 52-week Pivotal Study to Assess the Efficacy, Safety, and Tolerability of Dupilumab in Patients with Moderate-to-severe Chronic Obstructive Pulmonary Disease (COPD) with Type 2 inflammation [online]. [Accessed: 20.08.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-001954-91.

9. Sanofi-Aventis. A randomized, double-blind, placebo-controlled, parallel-group, 52-week pivotal study to assess the efficacy, safety, and tolerability of dupilumab in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) with type 2 inflammation (NOTUS); study EFC15805; clinical study report [unpublished]. 2023.

10. Sanofi. Pivotal Study to Assess the Efficacy, Safety and Tolerability of Dupilumab in Patients With Moderate to Severe COPD With Type 2 Inflammation (NOTUS) [online]. 2024 [Accessed: 20.08.204]. URL: https://clinicaltrials.gov/study/NCT04456673.

11. Bhatt SP, Rabe KF, Hanania NA et al. Dupilumab for COPD with Blood Eosinophil Evidence of Type 2 Inflammation. N Engl J Med 2024; 390(24): 2274-2283. https://doi.org/10.1056/NEJMoa2401304.

12. Sanofi. Dupixent 300 mg Injektionslösung in einer Fertigspritze; Dupixent 300 mg Injektionslösung im Fertigpen [online]. 2024 [Accessed: 10.09.2024]. URL: https://www.fachinfo.de.

13. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Fachgesellschaften. Nationale Versorgungsleitlinie COPD; Teilpublikation der Langfassung; 2. Auflage, Version 1 [online]. 2021 [Accessed: 30.09.2024]. URL: https://www.leitlinien.de/themen/copd/pdf/copd-2aufl-vers1.pdf.

14. Gemeinsamer Bundesausschuss. Niederschrift (finale Fassung) zum Beratungsgespräch gemäß § 8 Abs. 1 AM-NutzenV; Beratungsanforderung 2023-B-319; Dupilumab als Add-on-Erhaltungstherapie bei Erwachsenen mit chronisch obstruktiver Lungenerkrankung [unpublished]. 2024.

15. Global Initiative for Asthma. Global strategy for asthma management and prevention; revised 2014 [online]. 2014 [Accessed: 30.09.2024]. URL: https://ginasthma.org/wp-content/uploads/2019/01/2014-GINA.pdf.

16. Elpen. Fluticasonpropionat Elpen [online]. 2019 [Accessed: 18.09.2024]. URL: https://www.fachinfo.de.

17. GSK. Atmadisc Diskus [online]. 2020 [Accessed: 18.09.2024]. URL: https://www.fachinfo.de.

18. European Medicines Agency. Dupixent; Assessment report [online]. 2024 [Accessed: 17.09.2024]. URL: https://www.ema.europa.eu/en/documents/variation-report/dupixent-h-c-4390-ii-0079-epar-assessment-report-variation_en.pdf.

19. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstuctive pulmonary disease (2024 report) [online]. 2024. URL: https://goldcopd.org/wp-content/uploads/2024/02/GOLD-2024_v1.2-11Jan24_WMV.pdf.

20. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Fachgesellschaften. Nationale VersorgungsLeitlinie Asthma; Langfassung; Version 5.0 [online]. 2024. URL: https://register.awmf.org/assets/guidelines/nvl-002l_S3_Asthma_2024-08.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a24-79.html.