Dupilumab (COPD)

Addendum to Project A24-79 (dossier assessment)[1]

ADDENDUM

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50670 Köln
Germany

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

IQWiG employees involved in the addendum

- Sascha Abbas
- Michaela Florina Kerekes
- Jona Lilienthal
- Daniela Preukschat
- Claudia Selbach

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
COPD	chronic obstructive pulmonary disease
CRF	case report form
E-RS:COPD	Evaluating Respiratory Symptoms in COPD
EMA	European Medicines Agency
EXACT	Exacerbation of Chronic Pulmonary Disease Tool
FeNO	fraction of exhaled nitric oxide
FEV1	forced expiratory volume in 1 second
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
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
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
PDE4	phosphodiesterase type 4
post-BD	post-bronchodilator
PT	Preferred Term
RCT	randomized controlled trial
SABA	short-acting beta-2 agonist
SAE	serious adverse event
SAMA	short-acting muscarinic antagonist
SGB	Sozialgesetzbuch (Social Code Book)
SGRQ	St. George’s Respiratory Questionnaire
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

1 Background

On 10 December 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-79 (Dupilumab – Benefit assessment according to § 35a Social Code Book V) [1].

With its comments [2], the pharmaceutical company (hereinafter referred to as "the company") presented supplementary data, which went beyond the information provided in the dossier. The commission comprises the assessment of the data presented in the company's dossier [3] and the analyses presented by the company in the commenting procedure on:

- the data of the studies BOREAS and NOTUS presented in the dossier
- post hoc analyses for the outcome of St. George's Respiratory Questionnaire (SGRQ) (response criterion of 15%)
- subgroup analyses according to eosinophil count at baseline (< 300 versus ≥ 300 cells/µL)
- analyses of the sensitivity analysis on adverse events (AEs) of the BOREAS study presented in the dossier, taking into account events that occurred after the data cut-off of 8 February 2023
- post hoc analyses for the subpopulation with post-bronchodilator forced expiratory volume in 1 second (post-BD FEV1) ≥ 50% predicted with regard to adjustment of concomitant medication after exacerbations
- analyses of the subpopulation with post-BD FEV1 ≥ 50% predicted, intended to determine, as a first approximation, the proportion of patients who might have been eligible for treatment with roflumilast during the course of the study
- breakdowns of the inhaled corticosteroid (ICS) dosing information for the drugs and drug combination medication used

In accordance with the commission, the data announced in the oral hearing [4] and the data submitted by the company following the hearing [5] on the following aspects should also be taken into account:

- comparison of the dosages used in the BOREAS and NOTUS studies with the drugs and dosages approved in Germany
- analyses of serious adverse events (SAEs) that exclude both the Preferred Term (PT) chronic obstructive pulmonary disease (COPD) and chronic bronchitis as well as exacerbations

- analyses of the prespecified territory subgroup
- responder analysis with 15% response criterion for the Evaluating Respiratory Symptoms in COPD (E-RS:COPD)

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Information retrieval and study pool

A detailed description of the information retrieval as well as of the studies BOREAS [6-9] and NOTUS [10-13] can be found in dossier assessment A24-79 [1]. Both studies are double-blind randomized controlled trials (RCTs) comparing dupilumab with placebo. They included adult patients with moderate to severe COPD. The uncertainties described in the dossier assessment have been resolved after the commenting procedure insofar as the subpopulations presented by the company (relevant subpopulations of the BOREAS and NOTUS studies with post-BD FEV1 ≥ 50%) are now used for the benefit assessment in the present addendum. The background and remaining uncertainties affecting the certainty of conclusions are described below.

2.1.1 Suitability of the studies for conclusions on patients with COPD characterized by raised blood eosinophils

The patients in this therapeutic indication are a group of patients with COPD characterized by raised blood eosinophils. During the oral hearing, it was discussed to what extent the identification of patients with raised eosinophils in BOREAS and NOTUS reflects the approach in Germany [4]. The Summary of Product Characteristics (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 [14]. The current GOLD Report 2025 mentions a threshold value of ≥ 300 cells/µL eosinophils in the blood, but does not address the frequency of the measurements [15]. 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 during the screening phase 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 dossier assessment A24-79; I Appendix B, Table 8 [1]). 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 detecting raised blood eosinophils is adequate or which procedure will be implemented in the German health care context. 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. During the oral hearing, clinicians described that a second measurement is generally performed if only one value is available [4]. In its comments, the company presented subgroup analyses according to blood eosinophils at baseline (< 300 cells/µL versus ≥ 300 cells/µL). Due to the inclusion criterion of a single increase of ≥ 300 cells/µL at screening required in the studies, this subgroup characteristic (at baseline) reflects an increase of ≥ 300 cells/µL in one versus 2 measurements. In the present

situation, this subgroup characteristic is considered as part of the subgroup analyses (see Section 2.2.4).

Besides blood eosinophil count, the fraction of exhaled nitric oxide (FeNO) is another biomarker of type 2 inflammation, which is of key importance in the mechanism of action of dupilumab. In the therapeutic indication of asthma, dupilumab is approved for patients with severe asthma with type 2 inflammation, characterized by raised blood eosinophils and/or raised FeNO. Against the background of the patient group that is difficult to differentiate in the present therapeutic indication and the significance of type 2 inflammation for dupilumab, FeNO is also considered as a subgroup characteristic in addition to increased eosinophilia (see Section 2.2.4).

2.1.2 SPC-compliant use of concomitant medication in BOREAS and NOTUS

Dossier assessment A24-79 described that no information was available on the respective dosages of maintenance therapy with long-acting beta-2 agonists (LABA), long-acting muscarinic antagonists (LAMA) and inhaled corticosteroids (ICS) administered in both study arms of each BOREAS and NOTUS. With its comments, the company submitted dosing information for ICS as fluticasone propionate equivalents [2]. Following the oral hearing, the company also subsequently submitted dosing information for the respective ICS drugs (without conversion to fluticasone propionate equivalents) as well as for LABA and LAMA [5]. Thus, after the oral hearing, dosing information is available for all drugs of the concomitant medication. According to the company, the proportion of patients in the relevant subpopulation who received approval-compliant treatment with the concomitant medication was 82.6% across both studies. A review of the data is difficult insofar as it is unclear which dose range the company used for the individual drugs as a basis for the assessment of SPC-compliant administration. In addition, in its dosing information, the company did not differentiate between the administration of single and combination products, for which different dosing information is available depending on the SPCs (e.g. budesonide 400 to 800 µg/day with maximum doses of up to 1600 µg/day as monoproduct [16] and 640 µg/day in the combination product [17]). A review of individual drugs shows that the company incorrectly assessed some drugs as approval-compliant in COPD. This is explained below with reference to fluticasone furoate and fluticasone propionate:

- Fluticasone furoate is dosed at 92 µg/day for COPD [18]. The SPC explicitly states that the dose of 184 µg/day, which is approved for asthma, is not indicated for COPD and is associated with a potential increased risk of pneumonia and systemic steroid-related side effects. However, the presented dosing information shows that the company assessed both dosages (92 µg/day and 184 µg/day) in COPD as compliant with the approval. This affected 11 patients (1.2%) in the relevant subpopulations across both studies with an administered dose of 184 µg/day fluticasone furoate (or 200 µg/day

measured dose), which was incorrectly classified by the company as compliant with the approval.

- According to the SPC, fluticasone propionate is dosed at 1000 µg/day for COPD [19]. The company's dosing information shows that in its analyses, the company classified doses of 3000, 1840, 1000, 500 and 250 µg/day as compliant with the approval for COPD. This concerned, for example, 1 patient each (0.1%) with an administered dose of 3000 µg/day or 1840 µg/day, as well as 4 patients (0.4%) with 250 µg/day, who were incorrectly classified by the company as being dosed in compliance with the approval. Besides the approval-compliant administration of 1000 µg/day, many patients were also treated with 500 µg/day, which is contrary to the approval, but were classified as approval-compliant by the company. According to the comments by the German Respiratory League, the high ICS dose of 1000 µg/day approved in Germany 20 years ago is not appropriate from today's perspective, while the approval in the United States at that time was already for 500 µg/day [20].

Overall, based on the company's subsequently submitted data on the dosing of concomitant therapy, it is assumed that the proportion of patients who were not treated in compliance with the SPC does not reach a level that would be an argument against using the studies or subpopulations for the benefit assessment. The remaining uncertainty regarding the proportion of patients who did not receive concomitant therapy for COPD in compliance with the approval is taken into account in the certainty of conclusions of the results of both studies (see Section 2.2.2).

2.1.3 Implementation of the appropriate comparator therapy in BOREAS and NOTUS

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 one 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.

2.1.3.1 Treatment with roflumilast

In BOREAS and NOTUS the initiation of treatment with phosphodiesterase type 4 (PDE4) inhibitors such as roflumilast – as a treatment component according to the appropriate comparator therapy (ACT) – was not permitted at the start of the study or during the course of the study. 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 these patients did not meet the SPC criteria for the use of roflumilast [21]. In the presented subpopulation of the 2 studies, the company assumed that the ACT was implemented for patients for whom treatment with roflumilast is not suitable. Dossier assessment A24-79 described that, nevertheless, there was still some uncertainty as to whether the subpopulation used by the company included patients for whom roflumilast was not an option at baseline but would have been an option during the study. In its comments [2], the company presented post hoc analyses which, as a first approximation according to the company, should determine the proportion of patients who might have been eligible for treatment with roflumilast in the course of the study. For this purpose, the company analysed the proportion of patients with a post-BD FEV1 < 50% predicted at least 6 weeks after a moderate or severe exacerbation. It justified this approach by stating that an exacerbation event leads to an adjustment of therapy due to the possible deterioration in lung function, and that in everyday clinical practice, treatment with roflumilast is not considered before a persistent loss of function. In relation to the subpopulation with post-BD FEV1 ≥ 50% predicted, 45 patients (4.9%) in BOREAS and NOTUS had a post-BD FEV1 < 50% predicted as a result of an exacerbation, according to the company. Overall, it can be assumed that the BOREAS and NOTUS subpopulations presented by the company do not contain a relevant proportion of patients who would have been eligible for treatment with roflumilast during the course of the study. Further aspects regarding the implementation of the ACT in the BOREAS and NOTUS subpopulations presented by the company are described in the following sections.

2.1.3.2 Dose adjustment of concomitant medication

As described in detail in dossier assessment A24-79, according to the inclusion criteria, patients in BOREAS and NOTUS had inadequately controlled COPD. In this situation, the guideline recommends treatment escalation [22]. 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 one severe or 2 moderate COPD exacerbations.

Treatment adjustment after exacerbations

In the comments, the company presented results on the adjustment of the study medication in the presented subpopulation. It compared the number of moderate or severe exacerbations with the number of moderate or severe exacerbations that led to an increase

in the number of concomitant medications and/or an increase in the daily dose. In the BOREAS study, 113 moderate or severe exacerbations occurred in the intervention versus 164 in the comparator arm, and 88 versus 148 in the NOTUS study. In the BOREAS study, the number and/or dose of concomitant medication was adjusted in 1 versus 4 exacerbations and in the NOTUS study in 0 versus 4 exacerbations. The option provided in the protocol to adjust the concomitant medication was therefore used in only a few cases.

Treatment escalation and de-escalation with ICS

As described in dossier assessment A24-79, 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. 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 was also uncertainty regarding the extent to which de-escalations were necessary and could not be implemented because the concomitant medication was to be continued unchanged. The submission of dose information after the oral hearing shows that different doses of frequently used ICS drugs such as budesonide and fluticasone propionate were administered in BOREAS and NOTUS. In BOREAS and NOTUS, budesonide was administered at dosages between 160 and 2000 µg/day, with many patients receiving dosages of 320, 640 or 800 µg/day. There were wide dosage ranges in BOREAS and NOTUS also for fluticasone propionate with a median (Q1; Q3) of 500 (250; 500) µg/day in the BOREAS study and a median (Q1; Q3) of 1000 (500; 1000) in the NOTUS study.

Several comments noted that escalation with ICS does not play a role in the therapeutic indication of COPD or, with reference to Rabe 2020 [23] (comparison of 320 µg/day with 640 µg/day budesonide in triple therapy), that higher doses have no added value. It should be noted that the specific patient group of interest here, with raised eosinophil count (≥ 300 cells/µL), constituted only a very small proportion of the population investigated in Rabe 2020. In asthma, however, escalation of the ICS dose is an undisputed option for adapting therapy. With reference to the guidelines, the Drug Commission of the German Medical Association additionally emphasized the importance of ICS de-escalation (discontinuation in the case of pneumonia, gradual reduction in the case of high-dose administration) in COPD [24]. In BOREAS and NOTUS, ICS was given in a wide range of dosage with partly high and partly low ICS doses. The recently published Virchow 2024 comment on dupilumab therapy in COPD also raised the question of whether patients in BOREAS and NOTUS could also be patients with asthma, partly due to the high ICS doses in some cases [25]. In view of the patient group that is difficult to differentiate in the present research question and the obviously high ICS dosage range in BOREAS and NOTUS, including dosages that are only approved for asthma, the question of adequate dosage and dosage adjustment of ICS in this patient group does not appear trivial. Overall, the missing option of unrestricted patient-

specific escalation and de-escalation of ICS in patients in BOREAS and NOTUS is still to be emphasized critically (see the effect on the certainty of conclusions in the conclusion section below).

The assessment of the ICS dosages should also take into account that, as mentioned above, the high ICS dosage of 1000 µg/day of fluticasone propionate approved in Germany is twice as high as the dosage approved in the United States (500 µg/day). To take into account potential regional differences in the treatment of patients, the subgroup characteristic of region (the subgroup characteristic of territory was not provided) is considered in the subgroup analyses in the present situation (see Section 2.2.4).

Non-drug interventions and other interventions to optimize therapy

According to the National Care Guideline, the patient's correct handling and inhalation technique should be checked regularly, especially if symptom control is inadequate [22]. It is unclear to what extent this option of treatment optimization had been exhausted at the start of BOREAS and NOTUS. In addition, due to the requirement to continue the existing medication unchanged in BOREAS and NOTUS, it can be assumed that there was no guideline-compliant optimization of the inhalation technique, if possible and necessary, by selecting an individually suitable system. Besides, no information is available on non-drug treatment approaches, such as patient training, strengthening exercises, respiratory physiotherapy and psychosocial interventions [22].

Conclusion

It is unclear to what extent all drug and non-drug treatment options, including optimization of inhalation techniques, had already been exhausted at the start of BOREAS and NOTUS. In addition, the options for adapting treatments in terms of escalation were severely limited during the study, and de-escalation was not provided for. These restrictions are taken into account in the certainty of conclusions of the results of both studies (see Section 2.2.2).

2.1.4 Data cut-offs

Study BOREAS

For the BOREAS study, results for all outcomes are available for the final analysis with prespecified data cut-off on 8 February 2023, after all patients had completed the 52-week treatment phase. In the dossier, the company also presented results on side effects in a sensitivity analysis for the data cut-off on 2 May 2023, after all patients had also completed the 12-week follow-up phase (end of study). In the benefit assessment, the results of the final analysis are considered for all outcomes (see also Section 2.2.1, *Note on the results on side effects*).

Study NOTUS

The NOTUS study was completed in May 2024. According to the company, results of the final analysis, after all patients had completed the 52-week treatment phase, are not yet available. Protocol amendment 3 of 28 October 2023 introduced an interim analysis with the data cut-off on 29 September 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 the interim analysis was based on the results of the BOREAS study and in consultation with a regulatory authority. At the time of the interim analysis, not all patients had yet completed the 52-week treatment phase. In the relevant subpopulation, 76.5% of patients in the dupilumab arm and 80.1% in the placebo arm had completed the 52-week treatment phase or would have completed it by the time of the interim analysis if they had not discontinued treatment beforehand. The present benefit assessment uses the results from the interim analysis for all outcomes. According to the company's statements in the oral hearing, the final results are assumed to become available in 2025 [4].

2.1.5 Risk of bias across outcomes and transferability of the study results to the German health care context

Risk of bias across outcomes (study level)

Table 1 shows the risk of bias across outcomes (risk of bias at study level).

Table 1: Risk of bias across outcomes (study level) – RCT, direct comparison: dupilumab vs. placebo, subpopulation (post-BD FEV1 ≥ 50% predicted)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
BOREAS	Yes	Yes	Yes	Yes	Yes	Yes	Low
NOTUS	Yes	Yes	Yes	Yes	Yes	Yes	Low
Post-BD FEV1: post-bronchodilator forced expiratory volume in 1 second; RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for both studies.

Transferability of the study results to the German health care context

According to the company, around a quarter of the total population from both studies were recruited and treated in Western countries and the patient characteristics reflect everyday practice in Germany. The company explained that the median age was around 65.0 years, the majority of patients (87.4%) had white skin colour, slightly more than half were male (65.2%)

and all patients were former smokers (69.6%) or active smokers (30.4%). In addition, dupilumab administration in the studies was in compliance with the approval. According to the company, it can therefore be assumed that the study populations reflect the German health care context.

The company provided no further information on the transferability of the study results to the German health care context (for further aspects of transferability of the study results, see Section 2.1.1).

2.2 Results on added benefit

2.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - exacerbations
  - respiratory symptoms recorded with the E-RS:COPD
  - health status recorded with the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - recorded with the SGRQ
- Side effects
  - SAEs
  - discontinuation due to AEs
  - eye disorders (System Organ Class [SOC], AEs)
  - pneumonia (PT, AEs)
  - cardiovascular events (major adverse cardiovascular event [MACE])
  - other specific AEs, if any

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

Table 2 shows the outcomes for which data were available in the studies included.

Table 2: Matrix of outcomes – RCT, direct comparison: dupilumab vs. placebo, subpopulation (post-BD FEV1 ≥ 50% predicted)

Study	Outcomes										
	All-cause mortality[a]	Exacerbations[b]	Respiratory symptoms (E-RS:COPD)	Health status (EQ-5D VAS)	Health-related quality of life (SGRQ)	SAEs	Discontinuation due to AEs	Eye disorders (SOC, AEs)	Pneumonia (PT, AEs)	Cardiovascular events (MACE)	Other specific AEs
BOREAS	Yes	Yes	Yes	No[c]	Yes	Yes	Yes	No[d]	No[d]	Yes	No[e]
NOTUS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[d]	No[d]	Yes	No[e]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. The outcomes of moderate or severe exacerbations and severe exacerbations are considered.
c. The outcome was recorded only at randomization.
d. No data available for the relevant subpopulation.
e. No further specific AEs were identified based on the AEs occurring in the relevant studies.

AE: adverse event; COPD: chronic obstructive pulmonary disease; E-RS:COPD: Evaluating Respiratory Symptoms in COPD; MACE: major adverse cardiovascular event; post-BD FEV1: post-bronchodilator forced expiratory volume in 1 second; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; SOC: System Organ Class; VAS: visual analogue scale

Exacerbations

Exacerbations (adjudicated)

In BOREAS and NOTUS, exacerbations were documented by the investigator and confirmed by an external adjudication committee. According to the study protocol, exacerbations were categorized by severity as follows:

- moderate exacerbations: exacerbations that required either systemic corticosteroids (intramuscular, intravenous or oral) and/or antibiotics
- severe exacerbations: exacerbations that required hospitalization or monitoring in an intensive care unit for 24 hours, or that resulted in death

Except for the definition of severity classification, the study protocol contains no information on how an exacerbation was defined. According to the case report form (CRF), symptom changes could be documented as part of the exacerbation recording. Based on the information provided in the study protocol, it is unclear whether and how a worsening of symptoms was included in the recording of an exacerbation, however. In the commenting procedure, the company clarified the definition of exacerbation via the adjudication

committee in accordance with the "COPD exacerbations adjudication committee charter", which defined an adjudicated exacerbation as follows:

- An acute event of worsening respiratory symptoms going beyond normal day-to-day variability that leads to a change in medication. This usually involves an acute change in one or more of the following cardinal symptoms: i) increase in cough (frequency and severity), ii) increase in sputum production in volume and/or change in type of sputum, and iii) increase in dyspnoea.

The National Care Guideline COPD defines an exacerbation as an acute worsening of respiratory symptoms lasting at least 2 days with the need to intensify COPD therapy [22]. Based on the available information, it can be assumed overall that BOREAS and NOTUS used an adequate definition of exacerbation as a worsening of symptoms with the need to intensify COPD treatment.

Exacerbation of Chronic Pulmonary Disease Tool (EXACT)

In addition to the recording of adjudicated exacerbations via a worsening of symptoms with the need for intensification of COPD therapy (see above), exacerbations in BOREAS and NOTUS were recorded using the EXACT questionnaire. In a daily diary, the EXACT uses 14 questions to record respiratory symptoms relating to breathlessness, cough and sputum production as well as chest symptoms (11 questions) and an additional 3 questions to record insomnia, tiredness/weakness and psychological status (worried/scared about lung problems). The EXACT was designed with patient involvement to record exacerbations. The user manual defines an increase in EXACT total score from baseline by 12 points sustained for 2 days or 9 points for 3 days (scale range of 0 to 100). The baseline value is redetermined every 4 weeks in the absence of an exacerbation event according to EXACT or after an exacerbation according to EXACT has subsided [26]. The derivation of this definition for an exacerbation is not described in the manual. According to Leidy 2014, this definition is based on observations that the normal variability of the EXACT is 5 points and the variability in a medically treated exacerbation is 9 to 12 points [27]. Overall, it is not sufficiently certain whether the defined criteria capture a tangible deterioration. These scores are also below the response threshold of 15% of the scale range, although it is unclear how a suitable responder analysis could be carried out if the baseline value is redetermined on a recurring basis. In its assessment of the EXACT, the European Medicines Agency (EMA) also sees the lack of a common understanding of clinical important differences in the evaluation of the EXACT as a major point of criticism [28]. Furthermore, the National Care Guideline also defines an exacerbation not only by the change in symptoms but also by the intensification of COPD treatment, which is not covered by the EXACT. The lack of consistency between results on exacerbations defined using the EXACT and results on exacerbations whose definitions also include the intensification of COPD therapy is also critically discussed by the EMA [28]. Overall, there is insufficient information

to show that the EXACT evaluation algorithm reflects exacerbations. In contrast, there are results on adjudicated exacerbations that are suitable for analysing the outcome of exacerbations. The EXACT results are presented as supplementary information in Appendix A.

Respiratory symptoms (E-RS:COPD)

The 11 EXACT questions on respiratory symptoms (see above) form an independent instrument, the E-RS:COPD, which measures changes in respiratory symptoms. The E-RS is used in the present benefit assessment to measure respiratory symptoms (improvement [response threshold of 15% of the scale range] at Week 52 compared with baseline).

Note on the results on side effects

Unknown proportion of disease-related events in SAEs

An unknown proportion of disease-related events (exacerbations that were also classified as SAEs) was included in the analyses for the outcome of SAEs in both studies. Following the oral hearing, the company was asked to provide analyses of SAEs that excluded both the PTs COPD and chronic bronchitis and exacerbations. According to the information subsequently submitted for the company's written comments, no further PTs that are clearly attributable to COPD exacerbations were recorded besides these 2 PTs already excluded in the dossier [5]. For the relevant subpopulation, information on the individual PTs included in the analyses of SAEs is only available for events that occurred in ≥ 10 patients in at least one study arm. However, it is clear from the information in the study documents for the overall populations of BOREAS and NOTUS that several additional PTs that are potentially attributable to exacerbations (e.g. acute respiratory failure, pneumothorax or bronchospasm) were included in the analyses, particularly in the BOREAS study. This is taken into account in the risk of bias for the outcome of SAEs (see Section 2.2.2).

Events in the follow-up phase

Study BOREAS

All events that occurred during the follow-up phase of the BOREAS study were also included in the present analyses of side effects. At the present data cut-off (8 February 2023), after all patients had completed the 52-week treatment phase, almost all patients had also already completed the 12-week follow-up phase. In relation to the subpopulation of patients with post-BD FEV1 ≥ 50%, only 13 (5.4%) patients in the dupilumab arm and 17 (7.4%) patients in the placebo arm were still undergoing follow-up. In the study, patients in both study arms continued to receive their background medication during follow-up, but dupilumab was discontinued in the intervention arm. According to the SPC, dupilumab is intended for long-term treatment, but consideration should be given to discontinuing treatment in patients who have shown no response after 52 weeks of treatment [14]. Thus, discontinuation of dupilumab after 52 weeks, regardless of the response, does not comply with the SPC. According to the

study protocol, all AEs from the first administration of the study medication until 98 days after the last administration of the study medication were included in the analyses of side effects. Analyses on AEs until Week 52 are not available. Overall, an unknown proportion of patients with AEs up to 98 days after discontinuation of dupilumab are therefore included in the available AE analyses. This is taken into account in the risk of bias for the outcomes of side effects (see Section 2.2.2).

Study NOTUS

Analogous to the BOREAS study, according to the study protocol, all AEs from the first administration of the study medication until 98 days after the last administration of the study medication were included in the analyses of side effects in the NOTUS study. Also in the NOTUS study, patients in both study arms continued to receive their background medication during follow-up, but dupilumab was discontinued in the intervention arm. In the total population, 70.9% of patients had completed study treatment, and 63.7% had completed both the treatment phase and the follow-up observation phase at the time of the interim analysis. Analyses on AEs until Week 52 are not available. An unknown proportion of patients with AEs up to 98 days after discontinuation of dupilumab are therefore included in the AE analyses. This is taken into account in the risk of bias for the outcomes of side effects (see Section 2.2.2).

2.2.2 Risk of bias

Table 3 describes the risk of bias for the results of the relevant outcomes.

Table 3: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: dupilumab vs. placebo, subpopulation (post-BD FEV1 ≥ 50% predicted)

Study	Study level	Outcomes										
		All-cause mortality[a]	Exacerbations[b]	Respiratory symptoms (E-ERS:COPD)	Health status (EQ-5D VAS)	Health-related quality of life (SGRQ)	SAEs	Discontinuation due to AEs	Eye disorders (SOC, AEs)	Pneumonia (PT, AEs)	Cardiovascular events (MACE)	Other specific AEs
BOREAS	L	L	L	H[c]	–[d]	L	H[e, f]	L	–[g]	–[g]	H[f]	–
NOTUS	L	L	L	H[c]	H[h]	L	H[e, f]	L	–[g]	–[g]	H[f]	–

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Moderate or severe exacerbations and severe exacerbations are considered.
c. Large proportion of patients who were rated as non-responders due to missing values (BOREAS: 17% vs. 17%, NOTUS: 23% vs. 20%).
d. The outcome was recorded only at randomization.
e. Unknown proportion of disease-related events, as exacerbations that were also classified as SAEs are not excluded (see Section 2.2.1).
f. Unknown proportion of patients with AEs up to 98 days after discontinuation of dupilumab in the available AE analyses (see Section 2.2.1).
g. No data available for the relevant subpopulation.
h. Large proportion of patients who were rated as non-responders due to missing values (18% vs. 19%).

AE: adverse event; COPD: chronic obstructive pulmonary disease; E-RS:COPD: Evaluating Respiratory Symptoms in COPD; MACE: major adverse cardiovascular event; post-BD FEV1: post-bronchodilator forced expiratory volume in 1 second; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias for the outcomes of all-cause mortality, exacerbations and health-related quality of life (SGRQ) for the BOREAS and NOTUS studies is rated as low. For the outcome of health status (EQ-5D VAS) (only recorded in the NOTUS study during the course of the study) and respiratory symptoms (E-RS:COPD), the risk of bias is rated as high due to the high proportion of patients who were classified as non-responders due to missing values (NOTUS: 18% versus 19% for the EQ-5D VAS; BOREAS: 17% versus 17% and NOTUS: 23% versus 20% for the E-RS:COPD). The risk of bias for the outcome of discontinuation due to AEs is rated as low. For the other side effect outcomes for which data are available for the relevant subpopulation (SAEs, cardiovascular events [MACE]), the risk of bias is rated as high, as an unknown proportion of patients with AEs up to 98 days after discontinuation of dupilumab is included in the available AE analyses (see Section 2.2.1). In addition, an unknown proportion of disease-

related events (exacerbations that were also classified as SAEs) are included in the analyses for the outcome of SAEs (see Section 2.2.1).

Certainty of conclusions

Due to the uncertainties described in Sections 2.1.2 and 2.1.3 regarding the SPC-compliant administration of concomitant medication and the implementation of the ACT in BOREAS and NOTUS, the certainty of conclusions for the results of all outcomes is notably reduced (regardless of a high or low risk of bias at outcome level). Therefore, based on the results of the meta-analyses of BOREAS and NOTUS, at most hints, e.g. of an added benefit, can be derived for all outcomes.

2.2.3 Results

For the benefit assessment, results from meta-analyses with a fixed effect based on individual patient data are available for the relevant subpopulations of BOREAS and NOTUS with post-BD FEV1 ≥ 50%. Both studies are very similar in terms of design and methods, as they were based on very similar protocols. In addition, the demographic and clinical characteristics of the patients in the subpopulations presented are sufficiently similar between the studies (see benefit assessment A24-79 [1]). A meta-analytical summary of both studies is appropriate; the meta-analytical summaries conducted by the company are used for the benefit assessment.

Table 4 and Table 5 summarize the results of the comparison of dupilumab with placebo 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. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The results on common AEs, SAEs, and discontinuations due to AEs for BOREAS and NOTUS are presented in Appendix B.

Table 4: Results (mortality, morbidity, side effects) – RCT, direct comparison: dupilumab vs. placebo, subpopulation with post-BD FEV1 ≥ 50% predicted (multipage table)

Outcome category Outcome Study	Dupilumab N	Dupilumab Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Dupilumab vs. placebo RR [95% CI]; p-value[a]
Mortality					
All-cause mortality[b]					
BOREAS	242	4 (1.7)	230	2 (0.9)	1.90 [0.35; 10.32]; 0.456
NOTUS	217	4 (1.8)	236	3 (1.3)	1.45 [0.33; 6.43]; 0.624
Total[c]					1.64 [0.54; 4.97]; 0.385
Morbidity					
Respiratory symptoms (E-RS:COPD, improvement at Week 52[d])					
Total score					
BOREAS	241	44 (18.3)	231	26 (11.3)	1.53 [0.98; 2.38]; 0.061
NOTUS[e]	166	28 (16.9)	189	32 (16.9)	1.03 [0.66; 1.61]; 0.882
Total[f]					1.21 [0.89; 1.64]; 0.215
Breathlessness					
BOREAS	241	56 (23.2)	231	31 (13.4)	1.58 [1.06; 2.36]
NOTUS[e]	166	35 (21.1)	189	39 (20.6)	1.04 [0.69; 1.55]
Total[f]					1.29 [0.98; 1.68]
Cough and sputum					
BOREAS	241	41 (17.0)	231	34 (14.7)	1.09 [0.72; 1.64]
NOTUS[e]	166	32 (19.3)	189	37 (19.6)	0.84 [0.56; 1.27]
Total[c]					0.95 [0.71; 1.27]
Chest symptoms					
BOREAS	241	43 (17.8)	231	31 (13.4)	1.17 [0.77; 1.78]
NOTUS[e]	166	28 (16.9)	189	34 (18.0)	0.92 [0.59; 1.43]
Total[f]					0.99 [0.74; 1.34]
Health status (EQ-5D VAS, improvement at Week 52[g])					
BOREAS	Outcome only recorded at randomization				
NOTUS[e]	166	50 (30.1)	189	35 (18.5)	1.32 [0.90; 1.95]; 0.155
Health-related quality of life					
SGRQ (total score[h], improvement at Week 52[g])					
BOREAS	241	77 (32.0)	231	55 (23.8)	1.36 [1.03; 1.80]; 0.029
NOTUS[e]	166	52 (31.3)	189	42 (22.2)	1.30 [0.93; 1.80]; 0.120
Total[c]					1.34 [1.09; 1.65]; 0.005

Table 4: Results (mortality, morbidity, side effects) – RCT, direct comparison: dupilumab vs. placebo, subpopulation with post-BD FEV1 ≥ 50% predicted (multipage table)

Outcome category Outcome Study	Dupilumab N	Dupilumab Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Dupilumab vs. placebo RR [95% CI]; p-value[a]
Side effects					
AEs (supplementary information)[i]					
BOREAS	242	185 (76.4)	230	177 (77.0)	–
NOTUS	217	144 (66.4)	236	154 (65.3)	–
SAEs[j]					
BOREAS	242	22 (9.1)	230	26 (11.3)	0.80 [0.47; 1.38]; 0.428
NOTUS	217	18 (8.3)	236	26 (11.0)	0.75 [0.42; 1.34]; 0.331
Total[c]					0.78 [0.53; 1.15]; 0.213
Discontinuation due to AEs					
BOREAS	242	8 (3.3)	230	7 (3.0)	1.09 [0.40; 2.95]; 0.871
NOTUS	217	10 (4.6)	236	7 (3.0)	1.55 [0.60; 4.02]; 0.363
Total[c]					1.31 [0.66; 2.61]; 0.436
Eye disorders (SOC, AEs)	No data for relevant subpopulation[k]				
Conjunctivitis (broad CMQ[l], AEs, supplementary)	No data for relevant subpopulation[m]				
Pneumonia (PT, AEs)	No data for relevant subpopulation[n]				
Cardiovascular events (MACE[o])					
BOREAS	242	3 (1.2)	230	5 (2.2)	0.57 [0.14; 2.37]; 0.439
NOTUS	217	1 (0.5)	236	3 (1.3)	0.36 [0.04; 3.48]; 0.378
Total[c]					0.50 [0.15; 1.64]; 0.251

Table 4: Results (mortality, morbidity, side effects) – RCT, direct comparison: dupilumab vs. placebo, subpopulation with post-BD FEV1 ≥ 50% predicted (multipage table)

Outcome category Outcome Study	Dupilumab N	Dupilumab Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Dupilumab vs. placebo RR [95% CI]; p-value[a]

a. RR, 95% CI and p-value from logistic regression model with treatment as covariate; health status and health-related quality of life, region, ICS dose at baseline, smoking status at screening and the corresponding baseline values as additional covariates for the outcomes of respiratory symptoms (E-RS:COPD); the study in each case as additional covariate for the IPD meta-analysis.
b. The results on all-cause mortality are based on the data on fatal AEs.
c. IPD meta-analysis.
d. A decrease in score by ≥ 6 points (total score), ≥ 2.55 points (breathlessness), ≥ 1.65 (cough and sputum), ≥ 1.8 points (chest symptoms) compared with baseline is considered a clinically relevant improvement (range of total score: 0 to 40, breathlessness: 0 to 17, cough and sputum: 0 to 11, chest symptoms: 0 to 12). Patients with missing values at Week 52 were rated as non-responders.
e. Included were only patients who completed the 52-week treatment phase or would have completed it if they had not discontinued treatment beforehand.
f. Despite statistically significant heterogeneity in the E-RS:COPD total score (p = 0.049), as well as in the subscales of breathlessness (p = 0.006) and chest symptoms (p = 0.046), the joint effect estimator is presented in the present data situation (see text below).
g. A score increase (EQ-5D VAS) or decrease (SGRQ) by ≥ 15 points from baseline is considered a clinically relevant improvement (scale range of both scales: 0 to 100). Patients with missing values at Week 52 were rated as non-responders.
h. No suitable responder analyses are available for the subscales of symptoms, activity and psychosocial impact.
i. Analysis excluding the disease-specific PTs “COPD”, “chronic bronchitis” and excluding exacerbations (with the exception of exacerbations that were also classified as SAEs).
j. Analysis excluding the disease-specific PTs “COPD”, “chronic bronchitis”; exacerbations that were also classified as SAEs were not excluded (see Section 2.2.1).
k. < 10 patients in both study arms; in the total population, 8 (1.7%) vs. 9 (1.9%) patients in the BOREAS study and 10 (2.1%) vs. 5 (1.1%) patients in the NOTUS study had at least one event.
l. Prespecified operationalization for conjunctivitis with 16 PTs.
m. < 10 patients in both study arms; in the total population, 5 (1.1%) vs. 9 (1.9%) patients in the BOREAS study and 10 (2.1%) vs. 4 (0.9%) patients in the NOTUS study had at least one event.
n. < 10 patients in both study arms; in the total population, 13 (2.8%) vs. 19 (4.0%) patients in the BOREAS study and 8 (1.7%) vs. 6 (1.3%) patients in the NOTUS study had at least one event.
o. Adjudicated; includes cardiovascular death, non-fatal myocardial infarction and non-fatal stroke; no data available for the individual components.

AE: adverse event; CI: confidence interval; CMQ: Custom MedDRA Query; COPD: chronic obstructive pulmonary disease; E-RS:COPD: Evaluating Respiratory Symptoms in COPD; IPD: individual patient data; MACE: major adverse cardiovascular event; n: number of patients with (at least one) event; N: number of analysed patients; post-BD FEV1: post-bronchodilator forced expiratory volume in 1 second; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SGRQ: St. George’s Respiratory Questionnaire; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Table 5: Results (morbidity: exacerbations) – RCT, direct comparison: dupilumab vs. placebo, subpopulation with post-BD FEV1 ≥ 50% predicted (multipage table)

Outcome category Outcome Study	Dupilumab		Placebo		Dupilumab vs. placebo
	N	Annualized exacerbation rate [95% CI][a]	N	Annualized exacerbation rate [95% CI][a]	Rate ratio [95% CI]; p-value[a]
Morbidity					
Annualized exacerbation rate (52 weeks)					
Moderate or severe exacerbations[b, c]					
BOREAS	241	0.54 [0.39; 0.73]	231	0.78 [0.59; 1.03]	0.69 [0.51; 0.93]; 0.014
NOTUS[d]	217	0.82 [0.56; 1.21]	236	1.35 [0.91; 2.02]	0.61 [0.43; 0.85]; 0.004
Total[e]					0.66 [0.53; 0.82]; < 0.001
Severe exacerbations[b, f]					
BOREAS	241	0.16 [0.09; 0.29]	231	0.17 [0.10; 0.30]	0.93 [0.57; 1.50]; 0.754
NOTUS[d]	217	0.04 [0.01; 0.12]	236	0.12 [0.05; 0.32]	0.34 [0.12; 0.97]; 0.045
Total[e]					0.44 [0.20; 0.99]; 0.047
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
Exacerbations (supplementary information, 52 weeks)					
Moderate or severe exacerbations[b, c]					
BOREAS	241	80 (33.2)	231	91 (39.4)	0.84 [0.66; 1.07]; 0.167[g]
NOTUS[d]	217	61 (28.1)	236	84 (35.6)	0.79 [0.60; 1.04]; 0.094[g]
Total					0.82 [0.68; 0.98]; 0.029[h]
Severe exacerbations[b, f]					
BOREAS	241	5 (2.1)	231	10 (4.3)	0.48 [0.17; 1.38]; 0.180[g]
NOTUS[d]	217	4 (1.8)	236	11 (4.7)	0.40 [0.13; 1.22]; 0.097[g]
Total					0.44 [0.20; 0.94]; 0.035[h]

Table 5: Results (morbidity: exacerbations) – RCT, direct comparison: dupilumab vs. placebo, subpopulation with post-BD FEV1 ≥ 50% predicted (multipage table)

Outcome category Outcome Study	Dupilumab		Placebo		Dupilumab vs. placebo
	N	Annualized exacerbation rate [95% CI][a]	N	Annualized exacerbation rate [95% CI][a]	Rate ratio [95% CI]; p-value[a]
a. Negative binomial regression model with treatment group, region, ICS dose at baseline, smoking status at screening, disease severity at baseline and number of moderate or severe exacerbations within 1 year before study entry as covariates, and log-transformed observation period as offset variable; the study as additional covariate for IPD meta-analysis; treatment effect determined using delta method. b. Exacerbations were adjudicated by an independent committee, which defined an exacerbation as an acute event of worsening respiratory symptoms going beyond normal day-to-day variability that leads to a change in medication. This usually involves an acute change in one or more of the following cardinal symptoms: i) increase in cough (frequency and severity), ii) increase in sputum production in volume and/or change in type of sputum, and iii) increase in dyspnoea. c. Exacerbations that required either systemic corticosteroids (intramuscular, intravenous or oral) and/or antibiotics (moderate), or that required hospitalization or observation for 24 hours in an emergency intensive care unit or resulted in death (severe). d. In the NOTUS study, not all patients had yet completed the 52-week treatment phase at the time of the interim analysis (in the total population, 20% of patients in both study arms, data for the subpopulation are not available). e. IPD meta-analysis. f. Exacerbations that required hospitalization or observation for 24 hours in an emergency intensive care unit or resulted in death. g. Institute's calculation: RR, CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [29]). h. Institute's calculation: meta-analysis with fixed effect (Mantel-Haenszel method). CI: confidence interval; CRF: case report form; CSZ: convexity, symmetry, z-score; FEV1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; IPD: individual patient data; n: number of patients with (at least one) event; N: number of analysed patients; post-BD FEV1: post-bronchodilator forced expiratory volume in 1 second; RCT: randomized controlled trial; RR: relative risk					

As described in Section 2.2.2, based on the results of the meta-analyses of BOREAS and NOTUS, at most hints, e.g. of an added benefit, can be derived for all outcomes.

Mortality

All-cause mortality

The meta-analysis showed no statistically significant difference between treatment groups for the outcome of all-cause mortality. There is no hint of an added benefit of dupilumab in comparison with LABA and LAMA and, if applicable, ICS; an added benefit is therefore not proven.

Morbidity

Exacerbations

The meta-analysis showed a statistically significant difference in favour of dupilumab compared with placebo for the outcome of moderate or severe exacerbations. There is a hint of an added benefit of dupilumab in comparison with LABA and LAMA and, if applicable, ICS.

The meta-analysis showed a statistically significant difference in favour of dupilumab compared with placebo for the outcome of severe exacerbations. There is a hint of an added benefit of dupilumab in comparison with LABA and LAMA and, if applicable, ICS.

Symptoms

Respiratory symptoms

For the outcome of respiratory symptoms, measured using the E-RS:COPD total score, there is heterogeneity between the results from BOREAS and NOTUS ($p = 0.049$). Since heterogeneous results were only found for this outcome, the overall assumption of a fixed-effect model is maintained and the result of the corresponding meta-analytical summary is also used to derive the added benefit for the outcome of respiratory symptoms.

The meta-analysis (like the individual studies) showed no statistically significant difference between treatment groups. There is no hint of an added benefit of dupilumab in comparison with LABA and LAMA and, if applicable, ICS; an added benefit is therefore not proven.

Health status

The NOTUS study showed no statistically significant difference between treatment groups for the outcome of health status, measured with the EQ-5D VAS. No data in the course of the study are available for the BOREAS study. There is no hint of an added benefit of dupilumab in comparison with LABA and LAMA and, if applicable, ICS; an added benefit is therefore not proven.

Health-related quality of life

SGRQ

The meta-analysis showed a statistically significant difference in favour of dupilumab compared with placebo for the outcome of SGRQ, measured using the SGRQ total score. There is a hint of an added benefit of dupilumab in comparison with LABA and LAMA and, if applicable, ICS (see also Section 2.2.4).

Side effects

SAEs

The meta-analysis showed no statistically significant difference between treatment groups for the outcome of SAEs. There is no hint of greater or lesser harm from dupilumab in comparison with LABA and LAMA and, if applicable, ICS; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome of discontinuation due to AEs. For this outcome, there is no hint of greater or lesser harm from dupilumab in comparison with LABA and LAMA and, if applicable, ICS; greater or lesser harm is therefore not proven.

Eye disorders (SOC, AEs), pneumonia (PT, AEs)

No data are available for the relevant subpopulation for the outcomes of eye disorders (SOC, AEs) and pneumonia (PT, AEs). For these outcomes, there is no hint of greater or lesser harm from dupilumab in comparison with LABA and LAMA and, if applicable, ICS; greater or lesser harm is therefore not proven.

Cardiovascular events (MACE)

The meta-analysis showed no statistically significant difference between treatment groups for the outcome of cardiovascular events (MACE). For this outcome, there is no hint of greater or lesser harm from dupilumab in comparison with LABA and LAMA and, if applicable, ICS; greater or lesser harm is therefore not proven.

2.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (female versus male)
- number of moderate or severe exacerbations within 1 year before screening (≤ 2 versus 3 versus ≥ 4)
- blood eosinophils at baseline (< 300 cells/µL versus ≥ 300 cells/µL)
- FeNO (< 20 ppb versus ≥ 20 ppb)
- region (Asia versus Latin America vs. Eastern Europe versus Western countries)

Except for the characteristic of blood eosinophils at baseline, the subgroup characteristics mentioned were defined a priori.

For SAEs, the results for the total population were rated as highly biased, as an unknown proportion of disease-related events (exacerbations that were also classified as SAEs) were included in the analyses. No subgroup analyses were considered for the outcome of SAEs, as the additional effect of this bias cannot be estimated in subgroup analyses, especially with small case numbers.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

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

Table 6: Subgroups (health-related quality of life) – RCT, direct comparison: dupilumab vs. placebo, subpopulation with post-BD FEV1 ≥ 50% predicted

Outcome	**Dupilumab**		**Placebo**		**Dupilumab vs. placebo**	
Characteristic **Study** **Subgroup**	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI][a]**	**p-value[a]**
Health-related quality of life						
SGRQ (total score, improvement at Week 52[b])						
Blood eosinophils at baseline [cells/µL]						
BOREAS						
< 300	85	20 (23.5)	91	24 (26.4)	0.75 [0.45; 1.26]	0.274
≥ 300	156	57 (36.5)	140	31 (22.1)	1.59 [1.11; 2.28]	0.012
NOTUS						
< 300	58	18 (31.0)	73	14 (19.2)	1.47 [0.81; 2.68]	0.204
≥ 300	108	34 (31.5)	116	28 (24.1)	1.27 [0.85; 1.90]	0.241
Total[c]					Interaction:	0.049
< 300					1.00 [0.70; 1.43]	0.986
≥ 300					1.48 [1.14; 1.93]	0.003

a. RR, 95% CI and p-value from logistic regression model with treatment as covariate; for the outcome of health-related quality of life additionally region, ICS dose at baseline, smoking status at screening and the corresponding baseline values as covariates; for the IPD meta-analysis additionally the study as covariate in each case.
b. A score decrease by ≥ 15 points from baseline is considered a clinically relevant improvement (scale range: 0 to 100).
c. IPD meta-analysis.

CI: confidence interval; ICS: inhaled corticosteroids; IPD: individual patient data; n: number of patients with (at least one) event; N: number of analysed patients; post-BD FEV1: post-bronchodilator forced expiratory volume in 1 second; RCT: randomized controlled trial; RR: relative risk; SGRQ: St. George's Respiratory Questionnaire

Health-related quality of life

SGRQ

There is an effect modification by the characteristic of blood eosinophils at baseline for the outcome of SGRQ.

No statistically significant difference between treatment groups was found in the group of patients with < 300 cells/µL at baseline.

A statistically significant difference in favour of dupilumab was found in the group of patients with ≥ 300 cells/µL at baseline.

Due to the required inclusion criterion of a single increase of ≥ 300 cells/µL at screening, this subgroup characteristic (at baseline) reflects an increase of ≥ 300 cells/µL in one versus 2 measurements. The results of this subgroup were primarily considered, as it is unclear how to determine the raised eosinophil count in patients in the therapeutic indication, in particular whether multiple measurements are necessary (see Section 2.1.1).

An effect modification for this subgroup characteristic was only shown in the outcome described above. Due to the lack of clarity described in Section 2.1.1 about which procedure is appropriate for determining a raised eosinophil count, the subgroup analyses were further examined in the present situation. This result was not confirmed when looking at the subgroup analyses of other outcomes without statistically significant interaction. In the outcome of severe exacerbations, for example, a statistically significant advantage of dupilumab was only found for the subgroup with < 300 cells/µL (p-value of the interaction test: 0.129).

Below, patients with a single measurement are therefore not considered separately from those with 2 measurements in the present situation.

2.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [30].

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

2.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.2 (see Table 7).

Determination of the outcome category for the outcome of moderate or severe exacerbations

The outcome of moderate or severe exacerbations is assigned to the outcome category of non-serious/non-severe symptoms/late complications, as the vast majority of the exacerbations included were moderate exacerbations.

Table 7: Extent of added benefit at outcome level: dupilumab vs. LABA and LAMA and, if applicable, ICS (multipage table)

Outcome category **Outcome**	**Dupilumab vs. placebo** **Proportion of events (%) or annualized rate** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	1.7%–1.8% vs. 0.9%–1.3%[c] RR: 1.64 [0.54; 4.97]; p = 0.385	Lesser/added benefit not proven
Morbidity		
Exacerbations		
Moderate or severe exacerbations (annualized rate)	0.54–0.82 vs. 0.78–1.35[c] Rate ratio: 0.66 [0.53; 0.82]; p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: "minor"
Severe exacerbations (annualized rate)	0.04–0.16 vs. 0.12–0.17[c] Rate ratio: 0.44 [0.20; 0.99]; p = 0.047 Probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Added benefit, extent: "minor"
Symptoms		
Respiratory symptoms (E-RS:COPD – total score), (improvement at Week 52)	16.9%–18.3% vs. 11.3%–16.9%[c] RR: 1.21 [0.89; 1.64]; p = 0.215	Lesser/added benefit not proven
Health status		
EQ-5D VAS (improvement at Week 52[d])	30.1% vs. 18.5% RR: 1.32 [0.90; 1.95]; p = 0.155	Lesser/added benefit not proven
Health-related quality of life		
SGRQ total score (improvement at Week 52)	31.3%–32.0% vs. 22.2%–23.8%[c] RR: 1.34 [1.09; 1.65] RR: 0.75 [0.61; 0.92][e]; p = 0.005 Probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: "minor"

Table 7: Extent of added benefit at outcome level: dupilumab vs. LABA and LAMA and, if applicable, ICS (multipage table)

Outcome category **Outcome**	**Dupilumab vs. placebo** **Proportion of events (%) or annualized rate** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	8.3%–9.1% vs. 11.0%–11.3%[c] RR: 0.78 [0.53; 1.15]; p = 0.213	Greater/lesser harm not proven
Discontinuation due to AE	3.3%–4.6% vs. 3.0%–3.0%[c] RR: 1.31 [0.66; 2.61]; p = 0.436	Greater/lesser harm not proven
Eye disorders (AEs)	No suitable data	Greater/lesser harm not proven
Pneumonia (AEs)	No suitable data	Greater/lesser harm not proven
Cardiovascular events (MACE)	0.5%–1.2% vs. 1.3%–2.2%[c] RR: 0.50 [0.15; 1.64]; p = 0.251	Greater/lesser harm not proven

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Minimum and maximum proportions of events or annualized rate in each treatment arm in the included studies.
d. Only recorded for the NOTUS study.
e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval: CI_u: upper limit of confidence interval; COPD: chronic obstructive pulmonary disease; MACE: major adverse cardiovascular event; RR: relative risk; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; VAS: visual analogue scale

2.3.2 Overall conclusion on added benefit

Table 8 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 8: Positive and negative effects from the assessment of dupilumab in comparison with the ACT

Positive effects	Negative effects
Non-serious/non-severe symptoms/late complications ▪ Moderate or severe exacerbations: hint of an added benefit – extent: “minor”	–
Serious/severe symptoms/late complications ▪ Severe exacerbations: hint of an added benefit – extent: “minor”	–
Health-related quality of life ▪ SGRQ: hint of an added benefit – extent: “minor”	–
ACT: appropriate comparator therapy; SGRQ: St George’s Respiratory Questionnaire	

Based on the subpopulation of BOREAS and NOTUS with post-BD FEV1 ≥ 50%, the present benefit assessment can draw conclusions only on those patients who are not eligible for treatment with roflumilast. No data in comparison with the ACT are available for patients who are eligible for treatment with roflumilast. The added benefit is therefore derived separately for these 2 patient groups.

Patients who are not eligible for treatment with roflumilast

Overall, only positive effects of dupilumab were found in comparison with the ACT. These positive effects, each with the extent “minor”, are present in the outcome categories of non-serious/non-severe and serious/severe symptoms/late complications, and health-related quality of life. Due to the uncertainties regarding the SPC-compliant administration of concomitant medication and the limited implementation of the ACT in BOREAS and NOTUS, there are only hints of an added benefit. In summary, there is a hint of minor added benefit of dupilumab in comparison with the ACT for 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, and who are not eligible for treatment with roflumilast.

Patients who are eligible for treatment with roflumilast

No suitable data are available in comparison with the ACT for 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, and who are eligible for treatment with roflumilast. For these patients, there is no hint of an added benefit of dupilumab in comparison with the ACT; an added benefit is therefore not proven.

2.4 Summary

As a result of the information subsequently submitted by the company in the commenting procedure, taking into account further commentators and the oral hearing, the studies BOREAS and NOTUS can be used for the benefit assessment and change the conclusion on the added benefit of dupilumab from dossier assessment A24-79.

The following Table 9 shows the result of the benefit assessment of dupilumab under consideration of dossier assessment A24-79 and the present addendum.

Table 9: 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]	Patients who are not eligible for treatment with roflumilast[d]: Hint of minor added benefit
		Patients who are eligible for treatment with roflumilast[d]: 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 [21].
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.

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Appendix A Results on exacerbations determined via EXACT

Table 10: Results (morbidity, supplementary information) – RCT, direct comparison: dupilumab vs. placebo, subpopulation with post-BD FEV1 ≥ 50% predicted

Outcome category Outcome Study	Dupilumab N	Dupilumab Annualized exacerbation rate [95% CI][a]	Placebo N	Placebo Annualized exacerbation rate [95% CI][a]	Dupilumab vs. placebo Rate ratio [95% CI]; p-value[a]
Morbidity					
Exacerbations determined via EXACT (52 weeks)					
BOREAS	241	0.72 [0.51; 1.02]	231	0.77 [0.55; 1.06]	0.94 [0.68; 1.30]; 0.725
NOTUS[b]	217	0.98 [0.63; 1.54]	236	1.03 [0.64; 1.65]	0.96 [0.69; 1.32]; 0.783
Total[c]					0.95 [0.76; 1.19]; 0.668
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
Exacerbations determined via EXACT (52 weeks)					
BOREAS	241	80 (33.2)	231	91 (39.4)	0.84 [0.66; 1.07]; 0.167[d]
NOTUS[b]	217	85 (39.2)	236	87 (36.9)	1.06 [0.84; 1.34]; 0.711[d]
Total					0.95 [0.80; 1.12]; 0.522[e]

a. Negative binomial regression model with treatment group, region, ICS dose at baseline, smoking status at screening, disease severity at baseline and number of moderate or severe exacerbations within 1 year before study entry as covariates and log-transformed observation period as offset variable; for IPD meta-analysis additionally the study as covariate.
b. In the NOTUS study, not all patients had completed the 52-week treatment phase at the time of the interim analysis (20% of patients in both study arms in the total population, data for the subpopulation are not available).
c. IPD meta-analysis.
d. Institute's calculation: RR, CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [29]).
e. Institute's calculation: meta-analysis with fixed effect (Mantel-Haenszel method).

CI: confidence interval; CSZ: convexity, symmetry, z-score; EXACT: Exacerbation of Chronic Pulmonary Disease Tool; FEV1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; IPD: individual patient data; n: number of patients with (at least one) event; N: number of analysed patients; post-BD FEV1: post-bronchodilator forced expiratory volume in 1 second; RCT: randomized controlled trial; RR: relative risk

Appendix B Results on side effects

For the overall rates of AEs and SAEs, the tables below present events for Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOCs) and PTs, each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- Overall rates of SAEs: events that occurred in at least 5% of patients in one study arm
- In addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 11: Common AEs[a] – RCT, direct comparison: dupilumab vs. placebo, subpopulation with post-BD FEV1 ≥ 50% predicted, BOREAS)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Dupilumab** **N = 242**	**Placebo** **N = 230**
Overall AE rate	185 (76.4)	179 (77.8)
Blood and lymphatic system disorders	11 (4.5)	9 (3.9)
Cardiac disorders	17 (7.0)	18 (7.8)
Gastrointestinal disorders	46 (19.0)	37 (16.1)
Diarrhoea	17 (7.0)	6 (2.6)
General disorders and administration site conditions	24 (9.9)	11 (4.8)
Infections and infestations	100 (41.3)	105 (45.7)
Bronchitis	8 (3.3)	12 (5.2)
COVID-19	10 (4.1)	13 (5.7)
Nasopharyngitis	20 (8.3)	24 (10.4)
Upper respiratory tract infection	22 (9.1)	23 (10.0)
Urinary tract infection	11 (4.5)	3 (1.3)
Injury, poisoning and procedural complications	31 (12.8)	39 (17.0)
Accidental overdose	10 (4.1)	15 (6.5)
Investigations	7 (2.9)	16 (7.0)
Metabolism and nutrition disorders	14 (5.8)	15 (6.5)
Musculoskeletal and connective tissue disorders	35 (14.5)	37 (16.1)
Arthralgia	7 (2.9)	11 (4.8)
Back pain	14 (5.8)	9 (3.9)
Nervous system disorders	35 (14.5)	28 (12.2)
Headache	25 (10.3)	13 (5.7)
Psychiatric disorders	4 (1.7)	11 (4.8)
Respiratory, thoracic and mediastinal disorders	34 (14.0)	37 (16.1)
Skin and subcutaneous tissue disorders	8 (3.3)	15 (6.5)
Vascular disorders	17 (7.0)	22 (9.6)
Hypertension	9 (3.7)	13 (5.7)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.1; SOC and PT notation taken without adaptation from Module 4 J.

AE: adverse event; COVID-19: coronavirus disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; post-BD FEV1: post-bronchodilator forced expiratory volume in 1 second; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 12: Common SAEs[a] – RCT, direct comparison: dupilumab vs. placebo, subpopulation with post-BD FEV1 ≥ 50% predicted, BOREAS)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Dupilumab** **N = 242**	**Placebo** **N = 230**
Overall SAE rate	27 (11.2)	30 (13.0)
Respiratory, thoracic and mediastinal disorders	10 (4.1)	14 (6.1)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.1; SOC and PT notation taken without adaptation from Module 4 J.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; post-BD FEV1: post-bronchodilator forced expiratory volume in 1 second; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 13: Discontinuations due to AEs, subpopulation with post-BD FEV1 ≥ 50% predicted, BOREAS – RCT, direct comparison: dupilumab vs. placebo

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Dupilumab** **N = 242**	**Placebo** **N = 230**
Overall rate of discontinuations due to AEs	8 (3.3)	7 (3.0)
Infections and infestations	1 (0.4)	3 (1.3)
Herpes zoster	1 (0.4)	0 (0)
COVID-19 pneumonia	0 (0)	1 (0.4)
Ophthalmic herpes zoster	0 (0)	1 (0.4)
Septic shock	0 (0)	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (2.1)	2 (0.9)
Bladder transitional cell carcinoma	1 (0.4)	0 (0)
Glioblastoma	1 (0.4)	0 (0)
Lung carcinoma cell type unspecified stage IV	1 (0.4)	0 (0)
Lung neoplasm malignant	1 (0.4)	0 (0)
Rectal cancer	1 (0.4)	0 (0)
Invasive ductal breast carcinoma	0 (0)	1 (0.4)
Pancreatic carcinoma metastatic	0 (0)	1 (0.4)
Nervous system disorders	1 (0.4)	0 (0)
Cerebral haemorrhage	1 (0.4)	0 (0)
Cardiac disorders	0 (0)	1 (0.4)
Acute myocardial infarction	0 (0)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	0 (0)	1 (0.4)
Chronic respiratory failure	0 (0)	1 (0.4)
Gastrointestinal disorders	1 (0.4)	0 (0)
Crohn’s disease	1 (0.4)	0 (0)

a. MedDRA version 25.1; SOC and PT notation taken without adaptation from Module 4 J.

AE: adverse event; COVID-19: coronavirus disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; post-BD FEV1: post-bronchodilator forced expiratory volume in 1 second; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 14: Common AEs[a] – RCT, direct comparison: dupilumab vs. placebo, subpopulation with post-BD FEV1 ≥ 50% predicted, NOTUS)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Dupilumab** **N = 217**	**Placebo** **N = 236**
Overall AE rate	145 (66.8)	158 (66.9)
Blood and lymphatic system disorders	4 (1.8)	10 (4.2)
Cardiac disorders	6 (2.8)	12 (5.1)
Gastrointestinal disorders	20 (9.2)	35 (14.8)
General disorders and administration site conditions	12 (5.5)	9 (3.8)
Infections and infestations	84 (38.7)	100 (42.4)
Bronchitis	9 (4.1)	12 (5.1)
COVID-19	21 (9.7)	23 (9.7)
Nasopharyngitis	10 (4.6)	21 (8.9)
Injury, poisoning and procedural complications	26 (12.0)	30 (12.7)
Accidental overdose	14 (6.5)	13 (5.5)
Metabolism and nutrition disorders	12 (5.5)	14 (5.9)
Musculoskeletal and connective tissue disorders	26 (12.0)	29 (12.3)
Back pain	11 (5.1)	8 (3.4)
Nervous system disorders	23 (10.6)	25 (10.6)
Headache	18 (8.3)	17 (7.2)
Respiratory, thoracic and mediastinal disorders	14 (6.5)	23 (9.7)
COPD	4 (1.8)	12 (5.1)
Vascular disorders	12 (5.5)	16 (6.8)
Hypertension	10 (4.6)	10 (4.2)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 26.0; SOC and PT notation taken without adaptation from Module 4 J.

AE: adverse event; COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; post-BD FEV1: post-bronchodilator forced expiratory volume in 1 second; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 15: Common SAEs[a] – RCT, direct comparison: dupilumab vs. placebo, subpopulation with post-BD FEV1 ≥ 50% predicted, NOTUS)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Dupilumab** **N = 217**	**Placebo** **N = 236**
Overall SAE rate	20 (9.2)	34 (14.4)
Respiratory, thoracic and mediastinal disorders	4 (1.8)	14 (5.9)
COPD	4 (1.8)	12 (5.1)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 26.0; SOC and PT notation taken without adaptation from Module 4 J.

COPD: chronic obstructive pulmonary disease; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; post-BD FEV1: post-bronchodilator forced expiratory volume in 1 second; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 16: Discontinuations due to AEs[a] – RCT, direct comparison: dupilumab vs. placebo, subpopulation with post-BD FEV1 ≥ 50% predicted, NOTUS)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Dupilumab** **N = 217**	**Placebo** **N = 236**
Overall rate of discontinuations due to AEs	10 (4.6)	7 (3.0)
Infections and infestations	4 (1.8)	0 (0)
COVID-19	1 (0.5)	0 (0)
Latent tuberculosis	1 (0.5)	0 (0)
Ophthalmic herpes zoster	1 (0.5)	0 (0)
Suspected COVID-19	1 (0.5)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.9)	2 (0.8)
Adenocarcinoma of colon	1 (0.5)	1 (0.4)
Papillary thyroid cancer	1 (0.5)	0 (0)
Prostate cancer	0 (0)	1 (0.4)
Blood and lymphatic system disorders	1 (0.5)	0 (0)
Autoimmune haemolytic anaemia	1 (0.5)	0 (0)
Nervous system disorders	0 (0)	1 (0.4)
Cerebrovascular accident	0 (0)	1 (0.4)
Cardiac disorders	1 (0.5)	1 (0.4)
Cardiogenic shock	1 (0.5)	0 (0)
Angina unstable	0 (0)	1 (0.4)
Skin and subcutaneous tissue disorders	1 (0.5)	1 (0.4)
Psoriasis	1 (0.5)	0 (0)
Dermatitis allergic	0 (0)	1 (0.4)
General disorders and administration site conditions	1 (0.5)	2 (0.8)
Sudden death	1 (0.5)	2 (0.8)

a. MedDRA version 26.0; SOC and PT notation taken without adaptation from Module 4 J.

AE: adverse event; COVID-19: coronavirus disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; post-BD FEV1: post-bronchodilator forced expiratory volume in 1 second; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class